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THE GENERAL RELATION BETWEEN SUSCEPTIBILITY AND PHYSIOLOGIC CONDITION *

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CHICAGO

The pharmacologist and the student of mammalian physiology find in general a high degree of apparent specificity in the susceptibility of different organs and parts to drugs and other external agents. For example, strychnin and atropin in certain concentrations are both excitants of the central nervous system, but strychnin is believed to act chiefly on the spinal centers, while atropin apparently affects chiefly the higher centers. Again, agaricin supposedly inhibits the terminations of the secretory fibers of sweat glands, but not, or to a lesser degree, other secretory terminations; but atropin is believed to inhibit not only the secretory terminations of the sweat glands, but also those of many others. Pilocarpin, on the other hand, supposedly excites the terminations of secretory nerves. The susceptibility of sensory nerves to cocain is apparently greater than that of motor nerves. In the susceptibilities of different parts of the nervous system and other organs to various anesthetics and narcotics, for example, ether, chloroform, morphin, nitrous oxid, etc., certain apparently more or less specific differences appear. The action of digitalin and related drugs on the heart and central nervous system and the action of ergot on the pregnant uterus are further cases in point.

Moreover, the susceptibility relations to a particular agent may differ greatly with different concentrations. A low concentration may excite a particular organ or part, a higher concentration may inhibit it. Certain concentrations may apparently be without effect on certain organs, although affecting others to a marked degree, while other concentrations may affect all. Of course, in the higher animals and man it is usually impossible to determine with any accuracy the concentration of an agent to which a particular internal organ is exposed at a given time. This is in general true whether the agent is introduced through the alimentary tract, the blood stream, the lymph, or from the body cavity. Some of the apparent specificities in the susceptibilities

* From the Hull Zoological Laboratory of the University of Chicago.

of different organs to certain agents are probably due to the fact that the different organs are actually subjected to widely different concentrations.

A distinction is often made between agents which affect only or chiefly certain organs or complexes, and the general protoplasmic poisons, such as the cyanids, the stronger acids, formaldehyd, phenol, salts of mercury and copper, etc. Many such agents are used as antiseptics. This distinction appears, however, to be chiefly, if not wholly, one of degree rather than of kind; for, so far as we know, any physical or chemical agent which acts on living protoplasm will become in sufficient concentration or intensity and with sufficient time a general protoplasmic poison, although the susceptibility to it of different species of organisms and of different organs may differ widely.

Without questioning the existence of the significance of specificities in susceptibility to external agents, particularly in the higher animals and man, it is my purpose to call attention to another aspect of the susceptibility problem which has become evident in the course of about twenty years of physiologic work on the lower invertebrates and on early developmental stages of both invertebrates and vertebrates. In these forms and stages we find a general and highly uniform relation in different individuals of the species and in different regions of the individual between susceptibility to many, perhaps to all, external agents in a certain range of concentration or intensity, and quantitative factors in physiologic or metabolic condition. Although this essentially quantitative relation between susceptibility and physiologic condition may undergo extensive modification in the course of development, particularly in the higher animals and man, it apparently constitutes the general physiologic foundation on which the more or less specific, or apparently specific, susceptibilities of the more highly specialized organs and parts develop.

I shall attempt to bring together in the form of a brief survey with references the more important facts and conclusions from this field of general physiology.

CRITERIA OF SUSCEPTIBILITY AND METHODS OF INVESTIGATION

With a certain range of concentration or intensity, susceptibility can be determined by survival time in many organisms. At all stages in many of the simpler organisms and in the earlier stages of development, even of the vertebrates, the occurrence of death through the action of a certain range of concentration or intensity of a large number of agents is closely associated with cellular disintegration or cytolysis.[1] Differences in susceptibility are indicated by differences in the time at

1. References 4, 6, 8, 11, 13, 19, 22, 32, 33, 35, 45, 51 and 52 in the literature cited.

which this process occurs. The cells of certain body regions or of certain individuals may lose their characteristic structure and break down completely, while those of other regions or individuals are still intact and show ciliary, contractile or other activity as evidence of life. With other agents or in other forms a coagulation of the protoplasm may serve as an indicator of death and so of susceptibility. Cessation of motor activity in motile forms, a certain degree of narcosis or of some other toxic effect of an agent can also be used in some cases as criteria of susceptibility.

In work of this sort with chemical agents it is of course necessary to provide so far as possible for equal exposure to the agent of different body regions which are to be tested. In naked aquatic forms with little differentiation of different regions of the body surface, for example, many flatworms, the free swimming blastulae, gastrulae and larval stages of many invertebrates, the susceptibilities of different regions of the surface to chemical agents can be directly determined without difficulty, in solutions of the agents. In more highly differentiated forms with internal organs, the susceptibilities of these organs to chemical agents cannot be directly determined simply by immersing the organism in the agent used, because the agent must pass through or disintegrate the surface of the body before it can act on the internal organs. In many of the lower invertebrates, this difficulty can be in part eliminated by exposing transverse cut surfaces from different levels of the body, or from the same levels of different individuals, and in some forms in which a cuticle or other nonliving layer covers the surface, transverse cut surfaces may also be used. In many of these cases, however, it can be shown by comparing the effects of various chemical and physical agents that regional differences in susceptibility are independent of the cuticle; for example, we may find that the differences are similar for extremes of temperature and lack of oxygen, on the one hand, and potassium cyanid or hydrochloric acid on the other. It is evident that with certain physical agents, such as extremes of temperature, the impermeability of a surface covering is not of importance.

In the investigation of susceptibility in early developmental stages it is also generally possible to make use of the action of external agents on the rate of development as well as of their directly lethal or toxic action. For example, the inhibiting or accelerating effect of different agents on different body regions may be determined and compared.[2]

These various ways of determining susceptibility are all modifications of what has been called the direct method, because the susceptibility is directly determined by the lethal, toxic or other action

2. References *2*, *3*, 14 and 19.

of the agent.[3] The range of concentration or intensity available for this method lies between that which is immediately lethal for all parts or individuals concerned and that which permits the acquirement of tolerance by some regions or individuals.

But susceptibility can also be determined indirectly; that is, by determining the ability to acclimate[4] or acquire tolerance to a certain low range of concentrations or intensities, not lethal within a short time, and by the ability to recover after temporary exposure to a nonlethal range. In mature forms such acclimation or recovery may be indicated by continuation of life, resumption of motor activity, increase in respiratory exchange after an initial decrease, or by other physiologic criteria. In early developmental stages it may also be indicated by increase in rate of growth or differentiation after an initial inhibition.[5] This method of investigating susceptibility through the ability to acclimate to, or to recover from, the action of an agent has been called the indirect method.[6]

To obtain adequate knowledge of the susceptibility of a particular organism to a particular agent in relation to physiologic condition it is necessary to work with a wide range of concentrations or intensities from those which are rapidly lethal to those which permit rapid acclimation or recovery by the most susceptible individuals or parts concerned. Moreover, some agents have different lethal or toxic actions in different concentrations. For example, mercuric chlorid in high concentrations "fixes" protoplasm, while in low concentration it disintegrates many protoplasms, and in still lower concentration it permits continuation of life and acclimation. Also the range of concentrations producing each of these effects differs in a definite way with differences in physiologic condition for different body regions of the individual and different individuals of the species. In a study of susceptibility of developmental stages of the frog to mercuric chlorid, it was found necessary to use concentrations ranging from $\frac{1}{5,000}$ to $\frac{1}{30,000,000}$ molar.

These various modifications of the direct and indirect methods of determining susceptibility make possible various checks on the results of any one of them. If, for example, a certain body region is killed earlier than others in a high concentration and its motor or respiratory

3. References 1, 2, 4, 6, 7, 8, 9, 11, 13, 14, 15, 16, 19, 22, 25, 32, 33, 35, 45, 51 and 52.

4. The terms "acclimate" and "acclimation" are used here in the general biologic sense denoting adjustment or equilibration to an environment. Acclimation, as the term is used in this paper, is essentially the same as acquirement of tolerance, except that in the work with the simpler organisms the agent is usually added directly to the normal environmental medium.

5. References 14 and 19.

6. References 4, 7, 9 Chap. III, and 14.

activity or its rate of growth and development are more inhibited than those of others in somewhat lower concentrations, the different lines of evidence serve to confirm each other. But the chief interest of the susceptibility method for general physiology is the wide field within which the regional differences in susceptibility within the individual and the individual differences within the species are nonspecific, or specific only to a slight degree, for particular agents. The factors concerned in these differences are discussed in the following sections.

EXPERIMENTAL DATA AND CONCLUSIONS

The general susceptibility relations have been studied in several hundred species of animals and plants. Stated briefly, the general conclusions are as follows: To a certain range of concentration or intensity of action of agent above the limit of acclimation and either lethal in the course of a few hours, or producing irreversible changes when exposure is continuous or changes only slowly reversible when exposure is temporary, susceptibility varies in general directly with, though not necessarily proportionally to, the rate of oxidative metabolism. To certain lower ranges of concentration or intensity of action the ability to acclimate or acquire tolerance varies in general directly with, though not proportionally to, the rate of oxidative metabolism. And finally, the ability to recover after temporary exposure to a certain range of concentration or intensity shows the same relation to oxidative metabolism.

In certain cases it has been possible to check the data on susceptibility by direct determination or colorimetric estimation of respiratory exchange of different body regions and individuals. In many other cases an indirect check has been obtained by comparison between susceptibility to potassium cyanid and the effect of this agent on oxygen consumption.[7] Regional and individual differences in rate and amount of reduction of potassium permanganate by protoplasm afford another check;[8] the indophenol reaction has proved useful in certain cases,[9] and differences in electric potential constitute at least an indicator of differences in physiologic condition.[10] In addition to these experimental methods, differences in rate of growth and development and of protoplasmic structure often serve as further indicators of difference in physiologic condition.[11] So far as facts are at hand, the evidence from all these different lines agrees for the earlier develop-

7. References 1, 7, 9 Chap. III to VIII, 23, 24, 34, 37, 38, 39, 40, 41, 42, 44, 46 and 47.
8. References 21 and 29.
9. Reference 8.
10. References 43 and 48.
11. Reference 10, Chap. III.

mental stages in general and for most of the simpler organisms, both animal and plant, throughout life. Exceptions and discrepancies have been shown in so many cases to be secondary results of the progress of differentiation and to be absent in the earlier developmental stages that we are justified in believing that for the protoplasm of a particular species the regional and individual differences in susceptibility depend primarily on quantitative factors in the protoplasm, and that the more or less specific relations between particular organs and particular agents which are characteristic of the higher animals and of man are secondary results of differentiation.

The following agents have been used thus far in work on susceptibility: potassium cyanid; various anesthetics including ethyl alcohol, ether, chloroform, choloretone, ethyl urethane, phenyl urethane, hydrochloric acid, sulphuric acid, acetic acid, sodium hydroxid, ammonium hydroxid, lithium chlorid, mercuric chlorid, copper sulphate, magnesium sulphate and many other electrolytes, the alkaloids caffein and strychnin, the "vital" dyes neutral red and methylene blue, hypotonic sea water for marine forms and distilled water for fresh water forms; the negative condition, lack of oxygen, extremes of temperature and light.[12] By no means all of these agents have been used on every form examined, but in practically all cases several of them have been used. Potassium cyanid and ammonium hydroxid have been extensively used; first, because their high toxicity makes it possible to work with very low concentrations; second, because the death changes produced by these agents in most protoplasms involve a disintegration of the cells which is readily observed; and third, in the case of potassium cyanid, because its inhibitory action on respiration and protoplasmic oxidation [13] gives the differences in susceptibility to cyanid an additional value as evidence of differences in oxidative rate.

It is scarcely necessary to say that for different species the concentrations or intensities and the time necessary for a particular effect differ widely. The protoplasm of each species has its own range of susceptibility and limits of acclimation and recovery and the order of effectiveness of different agents is not necessarily exactly the same for different species. That is to say, the susceptibility of each species-protoplasm, and perhaps to some degree that of each variety, race or pure line, is more or less specific, but the evidence indicates that within

12. Experiments with ultraviolet light and with light of the visible spectrum after sensitization of the organisms made at the Nela Research Laboratories by Dr. Marie Hinrichs under the direction of Dr. R. S. Lillie show the same general differences in susceptibility to light as to other agents. Through the kindness of the Nela Laboratories and Dr. Hinrichs I am permitted to mention here this unpublished work.

13. References 23, 34, 37, 41 and 44.

the species the differences in susceptibility depend in general primarily on quantitative differences in physiologic condition and only secondarily on the specific differences in the constitution of different organs and parts arising in the course of development.

THE PRIMARY REGIONAL AND INDIVIDUAL DIFFERENCES IN SUSCEPTIBILITY

In general, the earliest stages of development following fertilization are periods of acceleration of oxidative metabolism, as has been shown by Warburg, Loeb, Meyerhof and others; but early in the development a maximum is reached, and from this time on the rate of oxidative metabolism shows, on the whole, a decrease with the further progress of development and the advance of physiologic age. The changes during development in susceptibility and the capacity for acclimation and recovery parallel in general these changes in metabolic rate.[14] In the development of many forms, however, the decrease in rate of oxidative metabolism is not uniform and continuous, but is interrupted by periods of increase in rate at certain stages of development. These periods of increase are determined by various factors; for example, the appearance of motor activity, rapid growth of certain parts, some forms of larval metamorphosis, sexual maturity or breeding periods and various other functional factors. In the simpler organisms these changes are paralleled by corresponding changes in susceptibility, except so far as the general susceptibility relations are complicated and altered by the appearance of more or less specific susceptibilities of particular organs to particular agents.

In the flatworm, *Planaria*, and in various other animals which do not die after a short period of starvation but live on their tissues and decrease in size, an increase in rate of respiratory exchange occurs in the more advanced stages of starvation. Susceptibility likewise increases, and after feeding is resumed the susceptibility and rate of respiration are equal to, or somewhat higher than, a growing well fed animal of the same size as the animal reduced by starvation.[15] Similarly, the reorganization of an isolated piece of *Planaria* and others of the simpler animals into a new complete individual, and many, if not all of the processes of asexual reproduction, are accompanied by an increase in rate of respiratory exchange and an increase in susceptibility.[16] In short, susceptibility gives a rough comparative measure of physiologic age and indicates the occurrence of rejuven-

14. References 7, 9, Chap. IV, V, VI and XV, 20, 39, 40 and 50.
15. References 7, 9 Chap. VII, 24, 38 and 42.
16. References 9 Chap. V and VI, and 39.

escence in early embryonic development in starvation, in reconstitution and in asexual reproduction as clearly as does the rate of respiratory exchange.

Within the individual the differences in susceptibility serve primarily as indicators of the chief physiologic axes. The evidence from susceptibility, checked and confirmed by experimental data on respiratory exchange, reduction of potassium permanganate, electric potential differences and by observational data on rate of cell division, differentiation and growth, indicates that a physiologic axis is primarily a gradient in rate of the fundamental metabolic reactions concerned in living, with which are associated corresponding gradients in aggregate condition of the protoplasm, permeability of membranes and probably also gradients in water content and various other factors in protoplasmic condition.[17] In the work on susceptibility these gradients are indicated, either directly by disintegration or other changes associated with toxic action of the agent, or indirectly by differences along an axis in ability to acclimate to or recover from the toxic action. A brief survey of the data concerning the polar axis will serve as an illustration of results obtained with the susceptibility method. All except perhaps some of the simplest organisms possess what is called physiologic polarity; that is, organs develop and are arranged in a definite order with reference to a line which we call the polar axis. One end of this axis becomes the apical end, or in bilateral animals, the head, the other the basal or posterior end. This polar axis appears primarily as a quantitative gradient in physiologic condition as indicated by differences in rate of respiratory exchange, reduction of potassium permanganate, electric potential differences and susceptibility. In this gradient, susceptibility to higher concentrations and intensities and capacity for acclimation to and recovery from action of lower concentrations and intensities is greatest at that end of the gradient or axis from which the apical end or head of the organism arises and decreases posteriorly. Here also the results of the susceptibility method parallel those obtained by other methods in indicating that the high end of the gradient, that is, the region of highest physiologic activity, becomes apical or anterior and that other organs along the axis are localized at particular levels of the gradient. During the course of development this simple primary gradient may undergo modification and complication through the appearance of new gradients as particular organs and parts develop, and in some cases the primary polar gradient may even disappear and be replaced by others. Nevertheless, among several hundred species of animals and plants, including representatives of all the great animal

17. References 2, 3, 4, 5, 6, 8, 9 Chap. IX, 10, 11, 13, 14, 15, 16, 17, 18, 19, 21, 22, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 43, 45, 46, 48, 49, 51 and 52.

groups, physiologic polarity has been found without exception to be represented by such a gradient in susceptibility to many different agents. So far as evidence is at hand, the same is true for axes of radial and bilateral symmetry and for axes of particular organs.

The question of the origin of such gradients cannot be considered at length here, but it may be noted that a large amount of experimental evidence, as well as the facts of development, show that in the final analysis the gradients arise through exposure of the protoplasm concerned to a quantitative differential in environmental conditions.[18] Such differentials may be either intra-organismic or external. By various experimental methods it is possible to establish new gradients in many cases and so to determine new axes of polarity and symmetry.

In consequence of the differential susceptibility along an axis it is possible to alter experimentally the slope of the gradient and even to obliterate it. In this way the course of development as regards polarity and symmetry can be modified and controlled, and these axes can be completely obliterated so that the organism becomes apolar or even anaxiate.[19] The evidence for nature, origin and modification of these axial physiologic gradients is given in the references cited in Footnote 17.

Since the early stages of development of the sea urchin and of closely related forms have served as material for considerable work on susceptibility, a brief statement of the more important results attained will serve to show what can be accomplished by means of the susceptibility methods. In the unfertilized egg and the cleavage stages a gradient in susceptibility is present, although the absence of visible landmarks in some stages makes it impossible to demonstrate completely that the gradient always represents the polar axis. But from the elongated blastula stage on there is no difficulty. The elongated blastula is an ovoid form consisting of a single layer of cells surrounding an internal cavity, the wall being slightly thicker at the basal than at the apical end. This minute larva swims by means of cilia, with the apical end in advance. The differential susceptibility of this blastula stage, as well as that of other stages, has been studied by means of the following agents in concentrations empirically determined: Potassium cyanid, ethyl alcohol, hydrochloric acid, acetic acid, potassium permanganate, sodium hydroxid, mercuric chlorid, copper sulphate, hypotonic sea water, neutral red and crowding (lack of oxygen or accumulation of carbon dioxid). In a certain range of concentration of all these agents the toxic action, as indicated by cytolytic change or disintegration of the cells, occurs first at the apical

18. Reference 27, Chap. III.
19. Reference 14.

end and progresses basipetally. In somewhat later stages, as bilaterality develops, the basipetal progress of death is most rapid along that meridian which later becomes the anterior end of the larva. The method serves further not only to demonstrate the existence of the axial gradients, but also in many cases to pick out regions of rapid growth as they arise in development. In the more advanced stages, however, the possibility of modification of the primary quantitative relations by the appearance of specific susceptibilities exists, although it is practically excluded when similar results are obtained with a large number of different agents. Motor activity increases and quiescence decreases susceptibility. These data on the sea urchin have been published only in part.[20]

But instead of using the agents to kill, we may also investigate sea urchin susceptibility by subjecting early developmental stages to somewhat lower concentrations of agents, or for certain periods of time, and observing the modifications of development which occur. I have performed experiments of this kind with all the agents mentioned above [19] and Dr. J. W. MacArthur has performed such experiments with a large number of electrolytes, and in all cases it has been found that with certain ranges of concentration the development of the apical region is more inhibited than that of the basal region, and in later stages that of the median anterior region more than that of posterior and lateral regions. The most inhibited regions are smaller as compared with the normal than those less inhibited, or with the more extreme degrees of inhibition may fail entirely to develop. With concentrations permitting acclimation or recovery after temporary exposure, the apical and median anterior regions acclimate or recover more rapidly or more completely and so become relatively larger—as compared with the normal—than basal, posterior and lateral regions. By means of certain "stimulating" or accelerating agents in certain concentrations or intensities, for example, caffein (Hinrichs), a differential acceleration of development can be produced. In such cases apical and median anterior regions are more accelerated and relatively larger than basal, posterior and lateral regions. In these various ways modifications of form in two opposite directions and essentially similar in character for all the agents used can be obtained. The more extreme differential inhibitions are so different from the differential acclimations, recoveries and accelerations that they would not be recognized as belonging to the same species were their origins not known.[19] With a sufficient degree of differential inhibition bilaterality is obliterated or prevented from arising, and with a still greater degree polarity is also obliterated.[19]

20. Reference 11.

Work on modification of reconstitution in planarians,[21] on developmental modification in amphibia by Bellamy [22] and unpublished work on fishes by Mr. J. N. Gowanloch, as well as data on many other species, show that the differences in susceptibility are primarily similar in their relations to the chief body axes in very different organisms, both animals and plants, for certain ranges of concentration or intensity of all agents thus far used.

THE PHYSIOLOGIC BASIS OF GENERAL SUSCEPTIBILITY

The experimental data presented above may seem at first glance to be in direct conflict with the data from mammalian and human physiology and pharmacology, but it is my purpose to show that this is not the case.

In the first place, it is of course evident that external agents do not all act on living protoplasms in the same way. While our knowledge of the physicochemical changes concerned in the toxic or lethal action of any agent is far from complete, it is evident that different agents produce their effects in different ways. The action of acids and alkalis, of high and low extremes of temperature, of lack of oxygen and of accumulation of carbon dioxid cannot be identical. Again, the action of a heavy metal salt, such as mercuric chlorid, of various anesthetics, such as ether, chloroform, etc., of "stimulating" alkaloids, such as caffein, and of vital dyes, such as neutral red, must differ in many respects. Some agents may affect primarily the aggregate condition of the colloids, others the nature, concentration or balance of ions. Still others probably act primarily in one way or another on the lipoids; the action of some is chiefly osmotic; some may combine chemically with certain constituents of the protoplasm or enter into the chemical reactions of metabolism, and so on. Moreover, a particular agent may act differently on the protoplasms of different species or of different, highly specialized organs according to their constitution.

If we admit, as we must, these different possibilities of action, it is at once evident that the general susceptibility relations described in the preceding sections are quite independent of the specific character of the action of a particular agent. Moreover, the nonspecific character of the axial and regional differences in susceptibility within the individual and the individual differences within the species or race indicate that they depend primarily, not on the nature of the action of the various agents, but on some quantitative factor in the organism itself.

21. References 4, 12 and 28.
22. References 2 and 3.

In the light of present knowledge concerning permeability of protoplasmic membranes the possibility that differences in permeability may be responsible for at least some of the nonspecific differences in susceptibility at once suggests itself. As a matter of fact, axial, regional and individual differences in permeability to many agents undoubtedly exist. Gradients in penetration of vital dyes corresponding to the susceptibility gradients have been shown to exist in many forms,[23] and there are indications that similar penetration gradients for many other substances occur. But when we consider the data of susceptibility it is evident that differences in permeability will not account for all the facts as they stand. Even if we admit that the regions representing the higher levels of the axial gradients of susceptibility are in general more permeable than those representing the lower levels, there can still be no doubt that other factors than permeability are of fundamental importance in determining the susceptibility relations. In the first place, these relations are essentially similar in different organisms, both for agents such as vital dyes, which readily penetrate living protoplasmic membranes and exert their toxic action by accumulating within the cells, and for agents such as mercuric chlorid, which do not penetrate in appreciable quantities without killing or altering the membranes and their permeability. Moreover, the permeability of living membranes depends on the fact that they are alive, and living systems are dynamic, not static, that is, they are systems in which physicochemical changes are going on in or with approach to dynamic equilibrium. Therefore the permeability of living membranes must itself be in some measure an expression of the physicochemical activities, of the dynamic equilibrium or equilibration processes in the membranes. Consequently differences in permeability are generally associated with differences in rate of activity of living systems.

In the case of susceptibility to certain agents or conditions, however, permeability is not directly concerned. For example, the differences in susceptibility to lack of oxygen and to extremes of temperature can scarcely be regarded as due primarily to differences in permeability, yet they are in general similar to those observed with chemical agents. And finally, capacity for acclimation cannot be accounted for in terms of permeability, for the regions and individuals that are more susceptible to the more extreme degrees of action of the agents show greater capacity for acclimation to the less extreme degrees of action. If such regions or individuals are more permeable to the agents concerned, acclimation must occur, not because of, but in spite of, their higher permeability. In short, while differences in permeability

23. References 13, 15, 16, 26 and 51.

may be a factor in susceptibility to the direct toxic or lethal action of certain agents, it is evident that the nonspecific aspects of susceptibility in general cannot be accounted for in terms of permeability alone.

It has been stated above that the data at hand indicate a parallelism between susceptibility to toxic action and capacity for acclimation and recovery on the one hand and rate of oxidative metabolism on the other. Even if this be granted, it is evident that the oxidation-reduction reactions cannot be directly responsible for the parallel differences in susceptibility to so many different agents and conditions acting in so many different ways.

Where, then, shall we look for the physiologic basis of these general, nonspecific aspects of susceptibility? In view of all the facts, the only possible conclusion seems to be that the basis is to be found in a general relation between dynamic systems and external agents or conditions which produce disturbance or alteration of such systems. This general relation, which holds for nonliving as well as for living systems, may be stated for our purposes in the following terms: To disturbances producing in any manner alteration beyond the limits of equilibration or tolerance of the system and therefore leading to disruption or other irreversible change within a measurable period of time, the susceptibility must vary directly with, though not necessarily proportionally to, the rate of the changes characteristic of the system. On the other hand, to disturbances within the limits of equilibration, acclimation or tolerance, or to those producing changes which are reversible after the disturbance ceases to act, the ability of the system to equilibrate, acclimate or acquire tolerance must also vary directly with, though not necessarily proportionally to, the rate of activity within the system. The facts presented above force us to the conclusion that the susceptibility of living protoplasmic systems to certain degrees of external disturbance of at least many, if not of all, sorts is merely a special case of this general relation between dynamic systems and external disturbances.

On this basis the nonspecific character of the differences in susceptibility with respect to different agents receives a simple physicochemical interpretation. No matter in what particular way the agent acts, if the degree of action is adequate to produce death or irreversible change in a measurable period of time, the more active region or individual must be more susceptible, and if its action is within the limits of acclimation, tolerance or recovery, all of which are processes of dynamic equilibration, the more active region or individual will acclimate or recover more rapidly or more completely than the less active.

The parallelism between susceptibility, acclimation and recovery and rate of oxidative metabolism observed or indicated in cases thus

far examined does not necessarily mean that the external disturbing factor acts directly on the oxidation-reduction reactions. It merely means at most that the rate of these reactions is to some degree a measure of the activity of at least the less highly specialized protoplasmic systems, and it is primarily with such systems that we are concerned.

To what extent the apparently specific susceptibilities of particular organs to particular agents in the more highly specialized organisms and stages of development will be resolved by further experimental investigation into special cases of this general law of susceptibility, it is, of course, impossible to predict. Without considering details, it may be pointed out that various data indicate a higher susceptibility of the more anterior levels of the central nervous system to various agents, even in man and mammals; and in various axiate organs, such as the heart, there is also evidence of a gradient of susceptibility similar to that in the axes of simpler organisms. A particular organ or organ complex may have a specific protoplasmic constitution, but so do the protoplasms of different species, and the general law of susceptibility may apply within the specific organ in much the same way as within the species. On the other hand, it is by no means necessarily true, either for different species or for different organs, that the differences in susceptibility parallel the differences in rate of oxidative metabolism of their protoplasmic systems.

It must also be borne in mind that the simple axial gradients of earlier developmental stages may undergo many modifications or may even disappear in the course of development of the higher animals. In consequence of such modifications even the general nonspecific susceptibilities of different regions or parts may be very different in the mature animal from those in the early stages of development. Moreover, the occurrence of such modifications can be determined only by extensive experimental investigation of the various developmental stages.

The higher general susceptibility and the greater ability to acclimate and recover of the young as compared with the old organism are sufficiently evident in man and the mammals, and are taken into consideration in the administration of drugs in medical practice. Here the general parallelism between susceptibility, tolerance and recovery on the one hand, and rate of oxidative metabolism on the other, exists to some extent as in the simpler organisms.

It may be suggested also that the general law of susceptibility holds to some extent with respect to roentgen rays and radium, and particularly as regards the difference in susceptibility of the cancer cell and the other cells of the body. The cancer cell is an extremely active cell, being in this respect comparable to a physiologically young or embryonic

cell. To a sufficient degree of disturbance, therefore, we may expect to find it more susceptible than other cells of the body, and it should also possess greater ability to acclimate to or to recover from less extreme disturbances. Its high susceptibility to the action of radium may be, therefore, largely or wholly nonspecific and merely another special case under the general law.

In conclusion, one point must be emphasized, namely, that there is no necessary conflict between what has here been called the general law of susceptibility and the existence of specific relations between particular protoplasms, whether species or organs, and particular external agents. The susceptibility of each species to external disturbances is undoubtedly in some measure specific, as is the susceptibility of any other dynamic system, but within the species the general law of susceptibility holds except as relations may be modified by specialization. As species undergo specialization in the course of evolution, the susceptibilities of their protoplasms undoubtedly become more highly specific. Similarly, as organs undergo specialization in development, their susceptibilities undoubtedly attain a higher specificity. The general law of susceptibility concerns only one aspect, the nonspecific aspect of the relations between dynamic systems and external disturbances. So far as different kinds of systems exist in the different regions or organs of an organism, so far the possibility of specific differences in susceptibility exists. But within each particular kind of system the general law may still hold, its validity being again limited by specialization of the various parts of such a system into systems of particular kinds.

SUMMARY

1. Evidence is presented in support of the conclusion that the susceptibility to action of external agents of the living protoplasms of different individuals of a species and of different regions of the individual depends primarily on quantitative differences in the individuals or regions concerned and that rate of oxidative metabolism is in some degree a measure of these differences. The evidence at hand indicates that susceptibility and capacity for acclimation and recovery vary in general directly with, though not necessarily proportionally to, the rate of oxidative metabolism.

2. This general law of susceptibility does not depend on the particular character of the action of a particular agent, but is a special case of the relation between dynamic systems and external disturbances. It has been shown to hold for the simpler organisms and for the earlier stages of development and does not exclude the possibility that the susceptibilities of different species protoplasms and of different specialized organs, particularly in the more highly differentiated forms, are specific.

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GASTRIC ULCER AND ACHLORHYDRIA

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Gastric and duodenal ulcer are frequently discussed under the heading of "peptic" ulcer, and there is no doubt that many of their hypothetical etiologic factors and clinical manifestations bring them into close relationship. The use of this general term, however, is by no means always advisable and leads to deductions that are not only confusing but erroneous. Statistics have been published under such a heading concerning the variations in the secretory and motor activities of the stomach, no attempt being made to discriminate between the two types of ulcer. Information thus obtained is valueless, for in these respects gastric and duodenal ulcers are markedly dissimilar. There is much evidence to support Hurst's [1] view that the motor activities of the stomach differ in the two conditions.

Since the introduction and widespread adoption of the fractional method of analysis of the gastric contents, it has become necessary to modify and even to abandon many of our former beliefs regarding the alterations in acidity in gastric and duodenal ulcer. This method, despite its present limitations and inaccuracies, supplies far more complete and reliable information than was obtained by means of the "one hour" test meal.

It was the general opinion that both types of ulcer were most frequently associated with a hyperacidity. Unquestionably, symptoms regarded as characteristic of this secretory disturbance were present in the majority of these cases, but the fact, as yet insufficiently appreciated, that these so-called symptoms of hyperacidity, including the immediate relief of abdominal distress obtained by taking alkalis, may occur in the complete and continued absence of free hydrochloric acid in the gastric contents, compels reconsideration of such a view.

Hurst,[2] in 1911, introduced 4 ounces (125 gm.) of 0.5 per cent. hydrochloric acid into the empty stomachs of six patients with proved gastric ulcers without producing any sensation. Bolton,[3] in 1913, stated that the pain of gastric ulcer did not bear any relation to the degree of acidity of the gastric contents, and might be relieved by food whether the acidity was normal or increased, and Carlson,[4] in 1918,

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confirmed this fact by investigations on a human subject. Moynihan [5] records his difficulty in convincing clinicians when "hyperacidity" or "acid dyspepsia" were such popular diagnoses that many of these cases were in fact cases of duodenal ulcer. He realized that many cases of duodenal ulcers occurred with diminished or normal stomach acidities. Gibson,[6] in 1911, showed in a series of proved cases that the acidity varied within wide limits.

In most instances, it is impossible to predict with any degree of certainty the state of the gastric acidity from a consideration of the symptoms alone. The results obtained by fractional gastric analysis have demonstrated that whereas duodenal ulcer is most frequently associated with an increased acidity, it is not uncommon to find low or normal acidities, thus confirming the views expressed by Moynihan and Gibson many years ago. Ascoli [7] states that hydrochloric acid may or may not be in excess in cases of duodenal ulcer, and if in excess the ulcers are usually recent. Gastric ulcer, on the other hand, is usually found to have diminished or even absent acidity. For this reason alone it is not always advisable to consider gastric and duodenal ulcer under the joint heading of peptic ulcer.

Cases are still recorded in which the actual presence of an ulcer is by no means certain. A diagnosis on clinical grounds alone, without positive roentgen-ray findings or actual demonstration of the ulcer by operation or postmortem, is not sufficiently reliable. This is especially true of gastric ulcer in which accurate clinical diagnosis is one of the greatest difficulty and uncertainty. The following series of gastric and duodenal ulcers consists of cases in which the ulcer had been seen either by roentgen-ray examination or at the time of operation. Of the twenty-seven cases of gastric ulcer, twenty-two had been demonstrated at operation and five seen as definite niches by roentgen-ray alone. Of the forty cases of duodenal ulcer, thirty-seven were proved by operation and three were seen by roentgen ray as persistent deformities of the duodenal cap. Adopting an arbitrary classification [8] based on a comparison between the curves of free acidity with the zone which included the curves of 80 per cent. of normal persons examined by Bennett and Ryle,[9] the results shown in Table 1 were obtained.

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"Achlorhydria" denotes no free hydrochloric acid present at any stage before or during digestion, using dimethylamidoazobenzol and congo red as indicators. "Hypochlorhydria" denotes that the curve of free acid at no stage exceeded 0.036 per cent of hydrochloric acid. It will be observed that 44.4 per cent. of gastric ulcers and 25 per cent. of duodenal ulcers had either diminished or absent free hydrochloric acid. A recent series of Moynihan's,[10] similarly classified, showed corresponding percentages of 47.2 and 22.4. Four (14.8 per cent.) of the gastric ulcer cases and one (1.5 per cent.) case of duodenal ulcer had complete achlorhydria, Moynihan's corresponding percentages being 13.1 and 5.5.

Crispin,[11] in 1916, from the Mayo Clinic, recorded eleven cases of duodenal ulcer with achlorhydria. They were all proved by operation, but only a single one-hour examination of the gastric contents was made. Furthermore, one case was associated with an empyema of the

Cases of Gastric and Duodenal Ulcer Classified According to Their "Acid Curves"

Type of Acid Curve	Gastric Ulcer		Duodenal Ulcer	
	Cases	Percentage	Cases	Percentage
Achlorhydria	4	14.8	1	2.5
Hypochlorhydria	3	11.1	0	0.0
Low normal	5	18.5	9	22.5
Normal	8	29.6	5	12.5
High normal	7	25.9	11	27.5
Hyperchlorhydria	0	0.0	14	35.0
Total	27	....	40	....

gallbladder and three with gastric ulcers; these should be disregarded, for gallbladder disease itself is frequently associated with achlorhydria, as Crispin himself observes, and gastric ulcer more commonly than duodenal ulcer. The remaining six cases represent less than 1 per cent. of the total number of duodenal ulcers demonstrated at operation. Horner [12] in eight cases of gastric ulcer and fifteen of duodenal ulcer, proved at operation, found no case of anacidity, but this is a small series. Hardt [13] refers to a case of gastric ulcer with "typical" symptoms, in which repeated gastric analyses failed to find any free hydrochloric acid. He does not state, however, whether the ulcer was proved to exist. Hunter [14] examined twenty cases of ulcer of the body of the

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stomach, all verified by operation or necropcy, by means of fractional gastric analysis. He found three (15 per cent.) had complete achlorhydria. None of fifteen cases of duodenal ulcer, similarly verified, showed achlorhydria. It would therefore appear that gastric ulcer is associated with achlorhydria in a proportion of cases by no means negligible and that achlorhydria may occasionally accompany duodenal ulcer.

The experimental work of Bolton [8] and others afforded support to the hypothesis that the healing of a gastric ulcer is retarded by hyperacidity. Bolton also found, however, in a series of nineteen guinea-pigs in which he had produced ulcers, that there was a diminution in the acidity in the early stages, and a return to normal when healing had commenced. Hardt [15] concludes from his work on dogs that "there is no 'hyperacidity' in the gastric juice following the experimental production of gastric ulcers." There is no justification for the assumption that hyperacidity is necessarily one of the factors in the production of gastric ulcer.

Modern medical treatment of peptic ulcers seeks to achieve a cure by (1) neutralizing the acidity of the stomach contents as continuously as possible, and (2) administering a physically nonirritating and chemically non-acid-provoking diet. These principles are applied indiscriminately to both gastric and duodenal ulcer. Complete and rapid relief of pain (more rapid and effectual in the case of duodenal than of gastric ulcer) almost invariably results, but that this is due to the neutralizing effect of the alkali is by no means certain. At present, no method of medical treatment gives more satisfactory results when efficiently employed, although it is not always rational. Hardt and Rivers [16] directed attention to the harmful effects which may occasionally arise during intensive alkaline therapy, owing to the production of an alkalosis, and many clinicians have had similar experiences. If an achlorhydria is originally present, the danger of alkalosis resulting is all the greater, and neutralization by alkali is entirely irrational. Smithies [17] puts forward the view that "when peptic ulcer exists, it is a matter of serious question whether the introduction into the stomach of sufficient alkali to neutralize hydrochloric acid is not injurious rather than beneficial," and Moynihan [10] pertinently asks "whether an 'acid' treatment of gastric ulcer would not be more rational than an 'alkaline' treatment" because "in cases in which a gastric ulcer has been proved

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16. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171 (Feb.) 1923.

17. Smithies, F.: Significance of Etiologic Factors in Treatment of Peptic Ulcer, J. A. M. A. **74**:1555 (June 5) 1920.

to exist a diminished acidity is far more common than an increased acidity." Such provocative suggestions should stimulate the development of a more efficacious form of medical treatment of gastric ulcer.

Some clinicians admit that a small percentage of patients with gastric ulcer have achlorhydria, but they consider that such cases do not present the same clinical symptoms as the "typical" gastric ulcer. So far as gastric ulcer has any typical symptoms, no such distinction can be drawn from a study of the cases here recorded. The first two cases described are representative of all.

REPORT OF CASES

CASE 1.—J. W. A., a man, aged 50, was admitted to the Leeds General Infirmary on Nov. 30, 1922, complaining of pain in the epigastrium. Until six years before, he had been perfectly well and free from indigestion; then pain in the upper epigastrium began to occur about one and a half hours after meals, and was relieved by taking food or sodium bicarbonate. It continued on and off for three months, and then disappeared completely for some weeks. Further similar attacks followed, and gradually the pain became an almost daily occurrence. Six weeks before admission the pain became more severe and extended to both hypochondriac regions and through to the back; it was of a dull, aching character and usually accompanied by nausea. Vomiting occurred on only three occasions with relief to the pain; the vomitus was sour tasting and burned his throat. The pain never awakened him during the night. He had always been very moderate in the use of alcohol and tobacco. His appetite was unimpaired, but he had lost twelve pounds in weight in the past year. Melena was never noticed, and no hematemesis occurred.

Examination.—The patient was well nourished and had good color. The teeth and gums showed moderate pyorrhea. The upper part of the abdomen was rigid, and tenderness in the midepigastrium was present on deep palpation. Roentgen-ray examination showed a stomach of normal size with no delay in emptying. A well marked persistent incisura was present high up near the esophageal opening, but there was no sign of a niche. Fractional test meal showed complete achlorhydria with a total acidity not exceeding 0.05 per cent. of hydrochrolic acid (Chart 1). Operation (Nov. 24, 1922): There was a chronic gastric ulcer on the posterior surface of the stomach, adherent to the pancreas; otherwise nothing abnormal was observed. Partial gastrectomy and gastrojejunostomy were performed. There was no evidence of malignancy on bistologic examination.

CASE 2.—A. E. H., a woman, aged 60, was admitted to the hospital on Dec. 1, 1922, complaining of attacks of pain in the epigastrium, which extended through to the back, for the last thirty-two years. She had had no previous illnesses of significance. The pain was frequently sharp and severe and came on about one hour after meals, but not regularly. Intervals of complete freedom from pain, usually lasting several weeks, alternated with the attacks. Twenty-three years before she had a severe melena and fainted, after which she was free from pain for seven years. Seven years ago she had had some gallstones removed, but the pain persisted. There had been no loss of appetite, and her weight had not altered greatly. Nausea accompanied the pain but not vomiting.

Examination.—The patient had a fairly well nourished appearance. Her teeth and gums were healthy. There was no abdominal rigidity, but tenderness in the epigastrium and in a small area to the left of the tenth dorsal vertebra posteriorly was elicited. A fractional test meal showed complete achlorhydria, with a total acidity not exceeding 0.077 per cent. of hydrochloric acid (Chart 2).

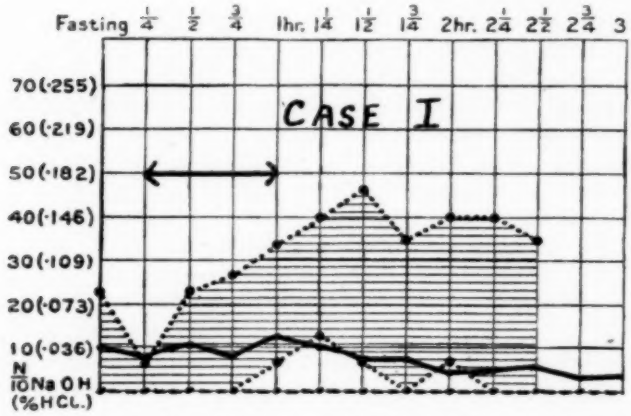

Chart 1.—Results of fractional test meal in Case 1. The shaded area represents the limits of free hydrochloric acid (dimethyl indicator) for 80 per cent. of normal people. The dot and dash line represents free hydrochloric acid; the continuous line represents total acidity; the arrow line represents food present in the stomach.

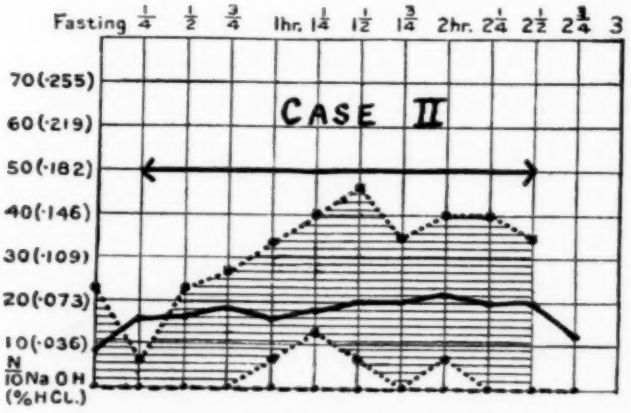

Chart 2.—Resuts of fractional test meal in Case 2.

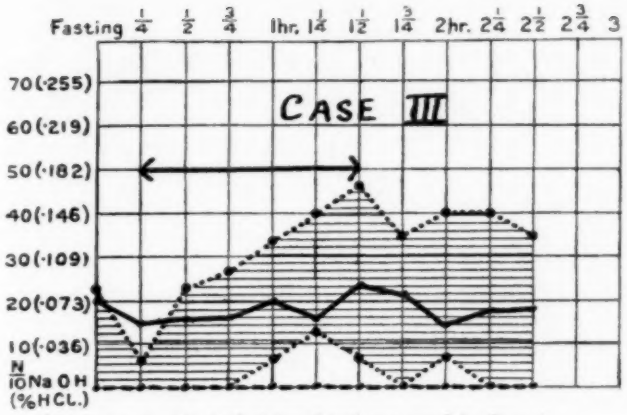

Chart 3.—Results of fractional test meal in Case 3.

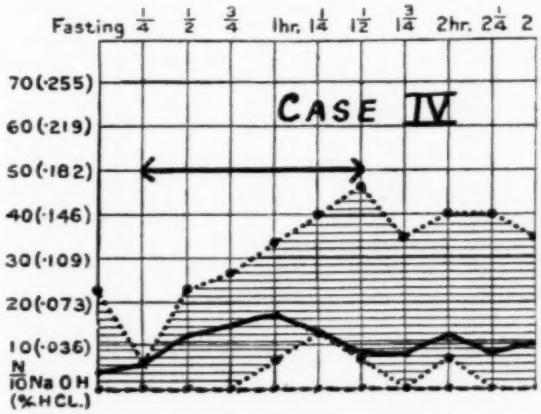

Chart 4.—Results of fractional test meal in Case 4.

Operation (Dec. 2, 1922) revealed dense adhesions everywhere and a small, very indurated gastric ulcer on the lesser curvature near the esophageal opening. The ulcer was cauterized, and posterior gastro-jejunostomy performed. (Microscopically, there was no evidence of malignancy.)

Case 3.—A fractional test meal given to E. B., a woman, aged 54, revealed complete achlorhydria with a total acidity not exceeding 0.091 per cent. of hydrochloric acid (Chart 3). Operation revealed definite pyloric obstruction. On the anterior wall of the pyloric antrum a chronic ulcer was found which was excised and a posterior gastro-jejunostomy performed. Otherwise nothing abnormal was observed. (There was no evidence of malignancy on histologic examination.)

Case 4.—A fractional test meal given to A. C., a woman, aged 51, showed complete achlorhydria, with a total acidity not exceeding 0.058 per cent. of hydrochloric acid (Chart 4). Operation revealed a chronic ulcer about half way along the lesser curvature. No other abnormality was observed. Partial

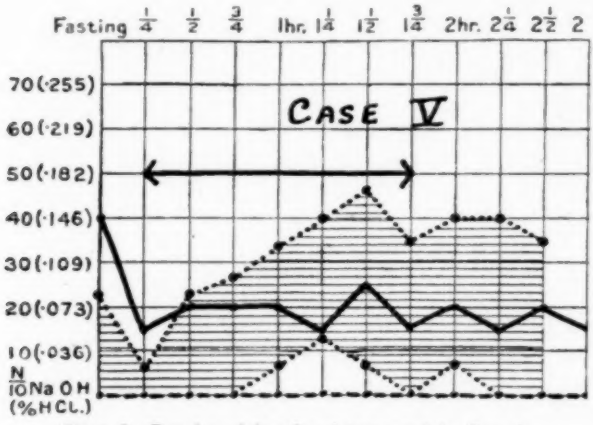

Chart 5.—Results of fractional test meal in Case 5.

gastrectomy and gastro-jejunostomy were performed. (Microscopically, there was no evidence of malignancy.)

Case 5.—A fractional test meal given to A. S., a woman, aged 39, showed complete achlorhydria, with a total acidity not exceeding 0.146 per cent. of hydrochloric acid (Chart 5). Operation revealed duodenal ulcer, but it was not dealt with, owing to an accompanying acute appendicitis for which appendicectomy was performed. (This patient had had a severe melena three years previously.)

COMMENT

A consideration of these cases shows that the achlorhydria is apparently not related to the situation or duration of the ulcer. They are indistinguishable clinically from ulcers associated with normal amounts of acid. Four of the five patients were females, and in this respect it is interesting to note that women tend to have lower gastric acidities than men as a general rule.

Whether the achlorhydria preceded the development of the ulcer or resulted secondarily is uncertain, but from the point of view of treatment the important fact is its presence. The methods of medical treatment in general use are probably more efficient than those employed twenty years ago, but they still leave much to be desired. The secretory disturbances are so varied and diminished acidity so frequent in gastric ulcer that it is doubtful whether they play an important part in the failure of the ulcer to heal. Medical treatment of gasric ulcer must needs attain a higher level of efficiency, and this cannot obtain while irrational methods, founded on misconceptions, are deemed satisfactory.

SUMMARY

1. Twenty-seven proved cases of chronic gastric ulcer were examined by means of the fractional test meal. Four (14.8 per cent.) had complete achlorhydria and three (11.1 per cent) had extremely low acidities.

2. Gastric ulcer is far more frequently associated with a diminished acidity than is duodenal ulcer, and it is exceptional to find complete achlorhydria with the latter.

3. These four cases of gastric ulcer were clinically indistinguishable from those associated with normal acidities. Neither the site nor the duration of the ulcer appeared to predispose to achlorhydria.

4. The methods in vogue in medical treatment of gastric ulcer, while producing many good results, are not wholly rational, and are based on misconceptions.

5. Recognition of the wide variations of secretory activity occurring in gastric and duodenal ulcer is essential for the efficient treatment of these conditions.

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE

I. AURICULAR FIBRILLATION *

L. N. KATZ, M.D., AND H. S. FEIL, M.D.

CLEVELAND

According to recent physiologic investigations (Wiggers [1]), ventricular systole may be divided into a period of isometric contraction and a period of ejection, the latter being again divided into a phase of maximum and reduced ejection. Recent studies on animals [2] have, moreover, shown how the duration of these phases as well as the duration of the entire systole is modified by a number of dynamic factors.[3] In brief, while the duration of the average systole is determined by the heart rate or average cardiac cycle—or more precisely the duration of any systole is determined by the duration of the previous diastole—it is also affected by other experimentally produced dynamic changes, namely, the specific effect of the cardiac nerves; the action of chemicals, drugs and hormones; changes in arterial resistance; and alterations in venous pressure. The isometric contraction period, for instance, is shortened by an increase in venous pressure and by the action of epinephrin or carbon dioxid and lengthened slightly by an increase in arterial resistance. Again, the ejection phase is shortened by an abbreviation of the previous diastole, by an increase in arterial resistance (when unassociated with any pronounced systolic retention), by a decrease in venous pressure, by the specific action of the accelerator nerves, and by the action of epinephrin and carbon dioxid. It is lengthened by a prolongation of the previous diastole, and by an increase in venous pressure (whether the result of an increased venous return or the back pressure effect of an increased systolic retention). Of the two phases, ejection is the more variable. In fact, the changes in the duration of systole are largely determined by the duration of the ejection phase. As a result, it was concluded that the duration of these phases depends on (*a*) the initial tension and diastolic volume of the ventricle, (*b*) the arterial resistance, and (*c*) the condition of the heart muscle.

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* From the Medical Clinic of Western Reserve University at City Hospital.

1. Wiggers, C. J.: Am. J. Physiol. **56**:415, 1921.

2. Wiggers, C. J., and Katz, L. N.: Am. J. Physiol. **53**:49, 1920. Katz, L. N.: J. Lab. & Clin. Med. **6**:291, 1921 Wiggers, C. J.: Am. J. Physiol. **56**:439, 1921. Wiggers, C. J., and Katz, L. N.: Am. J. Physiol. **58**:439, 1922.

3. The literature on this subject is reviewed in these reports.

How far are these physiologic influences responsible for the changes in the duration of systole in man? Previous studies have indicated their possible operation in normal persons. A few such instances may be cited. Lombard and Cope [4] expressed the relation of systole length to rate by a formula, the constant of which varied with sex, posture, etc. They therefore suggested venous return as an added factor. Wiggers and Clough [5] found that while the duration of systole in normal persons followed a curve plotted on the duration of the cycle in a general way, there were many exceptions. They reported, in addition, a relative lengthening of systole in "irritable hearts" and suggested a myocardial factor as being responsible for this. The results of Bowen,[6] after exercise, indicate a lengthening of systole independent of heart rate changes. Finally, at rapid heart rates the duration of systole has been found to be shorter than Lombard and Cope's formula would indicate.[7]

As many cardiovascular affections are accompanied by changes in venous pressure and arterial resistance as well as abnormalities in the innervation and condition of the heart muscle—changes comparable to those experimentally produced in animals—it seemed advisable to determine whether the duration of systole and its phases in such clinical cases is also governed by these physiologic mechanisms. The present report deals with observations in auricular fibrillation. This condition was selected because in auricular fibrillation we obtained clinical cases with varying degrees of venous pressure and a large variation in the length of consecutive cycles; we find varying degrees of cardiac failure and varying amounts of heart muscle involvement; and, finally, there is an absence of synergic auricular contractions.

METHOD

In order to obtain the required data, heart sounds and the subclavian pulse were registered simultaneously by Frank segment capsules (Wiggers' [8] adaptation). A typical record from a normal person is illustrated in Chart 1. The records (plates) were measured by a Lucas comparator, and only those which permitted accurate reading were selected. The isometric contraction period was measured by a slight modification of the method of Wiggers and Clough.[5] In our work, it was computed by subtracting the time interval between the upstroke

4. Lombard, W. P., and Cope, O. M.: Proc. Soc. Exper. Biol. & M. **16**:97, 1919; Am. J. Physiol. **45**:564, 1918; Ibid. **49**:139 and 150, 1919; Ibid. **51**:474, 1920.
5. Wiggers, C. J., and Clough, H. D.: J. Lab. & Clin. Med. **4**:644, 1919.
6. Bowen, W. D.: Am. J. Physiol. **11**:61, 1904.
7. Wiggers, C. J.: Personal communication.
8. Wiggers, C. J.: Circulation in Health and Disease, Ed. 2, Philadelphia, Lea & Febiger, 1923, p. 180.

of the subclavian pulse and the bottom of the incisura (Fig. 1, *a* to *c*) from the interval between the first and second sounds (Fig. 1, I to II). Ejection was readily computed from the subclavian pulse by the time interval between the upstroke and the beginning of the incisura (Fig. 1, *a* to *b*). The duration of diastole was obtained by subtracting the sum of the ejection and isometric periods, as determined above, from the interval between two successive second heart sounds (Fig. 1, II[1] to II). The latter was our criterion of cycle length, while the sum of ejection and isometric periods gave the duration of the total systole. In studying the effect of heart rate on systole, it was obviously preferable to use the preceding diastole rather than the succeeding one, as has been pointed out elsewhere.[9]

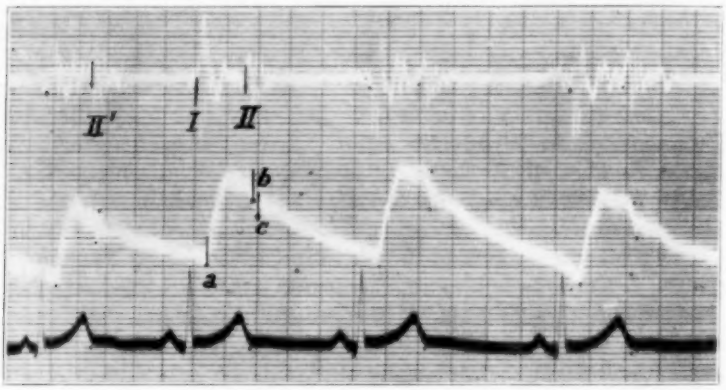

Fig. 1.—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) of normal person. I, beginning of first heart sound; II, II', this and the succeeding illustrations have been reduced two thirds; beginning of second heart sound; *a*, beginning of ejection; *b*, sharp drop of incisura; *c*, bottom of incisuria. Time in this and succeeding records is 0.2 of a second.

The records were obtained from ward patients. The diagnosis of auricular fibrillation was confirmed electrocardiographically. The cases were classified according to probable etiology into those with mitral valvulitis and those with myocardial fibrosis (or so-called chronic myocarditis). The absence or presence of cardiac failure was noted and, when present, the degree of failure ascertained. The nature and amount of therapy preceding the taking of the records and the blood pressure estimation at the time were also noted. Records were taken with the patient in the recumbent position and in most cases with respiration arrested.

9. Katz, L. N.: J. Lab. & Clin. Med. **6**:291, 1921.

DURATION OF SYSTOLE AND ITS PHASES IN NORMAL PERSONS

In studying the possible factors modifying the duration of systole and its phases in cases of auricular fibrillation, it is obviously necessary to compare them with normal subjects. Although the relation of systole length to heart rate, cycle length, etc., has been repeatedly investigated, it seemed desirable to test a small series of normal persons by our methods in order to be quite certain that they checked with those of previous observers. The data so obtained from fifteen normal adults, ranging in age from 20 to 30 years, is arranged in Table 1 according to the duration of the average cardiac cycle (Column III). This gives a range of cycle length from about 0.59 of a second, in Case 1, to 0.183 of a second in Case 15, comparable to heart rates ranging from 100 to 54 per minute (Column IV). In Column V is shown the duration of the previous diastole, and a little computation shows that this period increases with the cycle length, but not proportionately. This is due to the fact, shown in Column VI, that the duration of total systole also tends to increase as the cycle lengthens. In Columns VII and VIII are given the figures for the duration of the isometric contraction and ejection phases. A study of these figures shows a great variability in the duration of the isometric phase, a variability entirely independent of the duration of the cycle, previous diastole, total systole or ejection phase. The ejection phase, on the other hand, becomes longer, with but few exceptions, as the cycle lengthens.

Such relations show that in man, as in animals, the influence of heart rate or cycle length on the duration of systolic ejection is determined chiefly through the variation in the duration of diastolic filling, the ejection period progressively lengthening with longer diastoles, due to the greater amount of blood to be ejected in these beats.

The formula $S = 0.31\sqrt{C}$, for the recumbent position, which was evolved by one of us[9] from the formula $S = \frac{60}{K/R}$ of Lombard and Cope,[4] was tested in our series by calculating a theoretical "systole" (S) from the average cycle length (C) and comparing it with the average systole and ejection for that individual. The values for (S) which are given in Column IX, of Table 1, are shorter than the average total systole, except in Cases 6, 14, and 15 of this series (compare Column IX with VI). They are somewhat longer than the corresponding ejection period (compare Column IX with VIII). The results on the whole agree within limits with those of Lombard and Cope, for it should be remembered that their constant was used to measure ejection plus protodiastole (that is, upstroke to bottom of incisura of the carotid pulse) and not total systole. We should therefore compare the calculated S with ejection rather than with total

systole. It will be seen in Table 1 that the calculated S is actually greater than the ejection phase by a time interval varying from 0.008 to 0.064 of a second, or on the average 0.028 of a second, which is reasonably equivalent to the duration of protodiastole in man, as found by Burstein.[10]

In considering the variations of the phases of consecutive beats in one person, we find that diastole is always more variable than systole and that the systolic ejection, as a rule, varies more than the isometric period. Thus in Case 10, Table 1, in which twelve consecutive beats were measured, the duration of the previous diastole varies from the average by plus 0.076 and minus 0.039 of a second, while total systole varies from the average by plus 0.014 and minus 0.014 of a second (Columns V and VI). In the same case the variations from the average are plus 0.013 and minus 0.011 of a second for the ejection

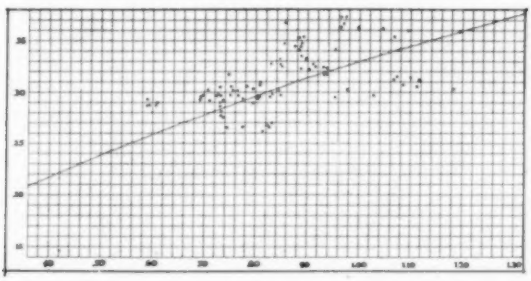

Fig. 2.—Plot showing the relation of total systole to corresponding cycle length in fifteen normal cases, and related to curve drawn from the formula $S = 0.31 \sqrt{C}$.

phase as compared with plus 0.005 and minus 0.004 of a second for the isometric period (Columns VII and VIII). A like consideration of other cases in the table will show similar relationships.

On plotting the relation of systole to cycle length according to the method of Wiggers and Clough,[5] as in Figure 2, it was found that although there was a definite relation between the individual systole and the corresponding cycle length, there were, however, occasional exceptions. These were no doubt due to the factors already referred to in the preliminary discussion, the result of such influences as respiration, change in the tonus of the cardiac nerves, etc.

Our findings, then, in normal persons are in accord with those of Lombard and Cope in a general way, and agree closely with the results of Wiggers and Clough. It may therefore be concluded that rate for

10. Burstein, J.: Am. J. Physiol. **65**:158, 1923.

TABLE I.—*Duration of Systole and Its Phases in Normal Persons*

I	II	III		IV	V		VI		VII		VIII		IX
Case	Number of Beats Measured	Duration of Cycle		Heart Rate	Duration of Previous Diastole		Duration of Total Systole		Duration of Isometric Contraction Period		Duration of Systolic Ejection Phase		Calculated Systole From Formula $S = 0.31\sqrt{C}$
		Average	Deviation From Average	60 / Average Cycle	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	
1. M. B.*.....	5	0.598	+0.010 −0.008	100	0.308	+0.010 −0.011	0.290	+0.003 −0.001	0.068	+0.002 −0.003	0.222	+0.002 −0.002	0.239
2. Ad.	5	0.753	+0.081 −0.025	80	0.471	+0.082 −0.031	0.282	+0.008 −0.006	0.040	+0.006 −0.003	0.242	+0.004 −0.005	0.269
3. We.	4	0.760	+0.017 −0.008	79	0.460	+0.024 −0.015	0.300	+0.007 −0.007	0.053	+0.007 −0.007	0.247	+0.001 −0.003	0.270
4. Al.	3	0.771	+0.093 −0.044	78	0.464	+0.030 −0.041	0.307	+0.003 −0.003	0.062	+0.001 −0.001	0.244	+0.002 −0.003	0.272
5. Ma.	3	0.792	+0.036 −0.026	76	0.494	+0.044 −0.025	0.298	+0.003 −0.003	0.031	+0.002 −0.002	0.267	+0.005 −0.004	0.276
6. Kel.	6	0.804	+0.030 −0.061	75	0.538	+0.025 −0.059	0.265	+0.004 −0.004	0.037	+0.002 −0.002	0.229	+0.003 −0.007	0.278
7. Kele.	6	0.809	+0.033 −0.012	74	0.512	+0.028 −0.018	0.297	+0.006 −0.007	0.060	+0.003 −0.004	0.237	+0.006 −0.003	0.279
8. J. W.	3	0.827	+0.019 −0.017	73	0.525	+0.023 −0.023	0.302	+0.006 −0.003	0.029	+0.004 −0.005	0.272	+0.002 −0.003	0.282
9. A. S.	4	0.869	+0.017 −0.012	70	0.515	+0.018 −0.024	0.354	+0.014 −0.008	0.067	+0.002 −0.003	0.267	+0.014 −0.008	0.289
10. J. P.	12	0.878	+0.078 −0.049	68	0.539	+0.076 −0.039	0.339	+0.014 −0.014	0.056	+0.005 −0.004	0.283	+0.013 −0.011	0.291
11. Er.	7	0.924	+0.010 −0.023	65	0.601	+0.014 −0.021	0.323	+0.005 −0.004	0.048	+0.006 −0.005	0.275	+0.002 −0.005	0.298
12. A. Se.	3	0.934	+0.166 −0.186	64	0.625	+0.171 −0.195	0.309	+0.005 −0.013	0.034	+0.008 −0.006	0.275	+0.015 −0.012	0.300
13. We.	8	1.011	+0.088 −0.046	59	0.646	+0.093 −0.053	0.365	+0.009 −0.011	0.078	+0.008 −0.008	0.287	+0.011 −0.013	0.312
14. R. W.†.....	4	1.087	+0.031 −0.063	55	0.778	+0.028 −0.052	0.309	+0.010 −0.021	0.050	+0.007 −0.011	0.259	+0.006 −0.004	0.322
15. At. S.‡.....	3	1.107	+0.076 −0.044	54	0.798	+0.083 −0.047	0.309	+0.005 −0.007	0.036	+0.006 −0.005	0.273	+0.006 −0.003	0.336

* Indicates female (all others male); Q-R-S-T interval 0.308 sec. (+0.008 to −0.007).
† Q-R-S-T interval, 0.429 sec. (+0.008 to −0.007).
‡ Q-R-S-T interval, 0.429 sec (+0.002 to −0.004).
The interval of time given is the average; the plus and minus figure represents the maximum and minimum deviation from this.

TABLE 2.—*Duration of Systole and Its Phases in Auricular Fibrillation*

I	II	III	IV	V	VI	VII	VIII	IX		X		XI		XII		XIII		XIV
								Duration of Cycle		Duration of Preceding Diastole		Duration of Total Systole		Duration of Isometric Contraction Period		Duration of Systolic Ejection Phase		
Case	Number of Beats Measured	Predominant Heart Rate	Maximum Systolic and Minimum Diastolic Blood Pressure	Age	Diagnosis	Cardiac Medication	Degree of Cardiac Failure	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Average	Deviation From Average	Calculated From Formula $S=0.31\sqrt{C}$
1. A. Fi.	34	186	128/ 85	68	My. F.	Dig.	++	0.323	+0.151 −0.158	0.200	+0.181 −0.087	0.123	+0.026 −0.027	0.037	+0.027 −0.022	0.086	+0.031 −0.031	0.176
2. C. Sp.	22	151	124/ 80	57	M. S.	0	++	0.397	+0.190 −0.144	0.222	+0.188 −0.098	0.175	+0.017 −0.042	0.047	+0.041 −0.038	0.128	+0.029 −0.056	0.195
3. R. Tl.	5	127	162/104	65	My. F.	0	—	0.470	+0.075 −0.078	0.175	+0.067 −0.030	0.275	+0.029 −0.028	0.081	+0.014 −0.019	0.194	+0.021 −0.019	0.213
4. H. Li.	7	114	210/120	72	My. F.	Dig.	++	0.525	+0.120 −0.180	0.302	+0.072 −0.119	0.223	+0.030 −0.028	0.062	+0.019 −0.011	0.161	+0.024 −0.044	0.225
5. H. Lea.*...	13	111	145/ 90	45	M. S.	0	—	0.540	+0.113 −0.119	0.307	+0.106 −0.118	0.233	+0.026 −0.023	0.036	+0.057 −0.021	0.194	+0.021 −0.049	0.228
6. M. Sk.	8	110	170/ ?	64	My. F.	Dig. Quin.	++	0.545	+0.377 −0.135	0.323	+0.354 −0.131	0.222	+0.023 −0.019	0.058	+0.025 −0.028	0.163	+0.037 −0.033	0.229
7. M. Gu.	5	98	162/ 80	70	My. F.	Dig.	±	0.610	+0.209 −0.148	0.331	+0.211 −0.144	0.279	+0.015 −0.016	0.073	+0.018 −0.018	0.206	+0.030 −0.022	0.242
8. D. Di.	6	96	140/ 80	47	M. S.	0	±	0.625	+0.047 −0.056	0.374	+0.030 −0.052	0.251	+0.031 −0.016	0.069	+0.021 −0.010	0.182	+0.072 −0.025	0.245
9. J. Kot. 11/16/22	15	94	110/ 90	36	M. S.	0	±	0.637	+0.151 −0.169	0.351	+0.161 −0.128	0.266	+0.037 −0.021	0.093	+0.037 −0.028	0.173	+0.037 −0.063	0.247
10. J. Kot. 7/2/22	12	93	110/ 90	36	M. S.	Dig.	+	0.640	+0.289 −0.252	0.398	+0.264 −0.223	0.242	+0.043 −0.053	0.061	+0.052 −0.055	0.181	+0.063 −0.081	0.248
11. V. Kr.	25	90	120/ 86	30	M. S.	0	—	0.664	+0.419 −0.172	0.420	+0.405 −0.134	0.244	+0.034 −0.038	0.044	+0.032 −0.020	0.200	+0.030 −0.032	0.253
12. Jo. Ber. ..	9	76	132/ 80	40	M. S.	Dig.	+++	0.787	+0.166 −0.062	0.478	+0.152 −0.056	0.309	+0.014 −0.015	0.119	+0.033 −0.025	0.196	+0.019 −0.019	0.275
13. Ju. Ben. ...	8	70	110/ 60	56	My. F.	Dig. Quin.	+	0.800	+0.144 −0.112	0.600	+0.144 −0.117	0.260	+0.018 −0.016	0.030	+0.015 −0.017	0.230	+0.008 −0.010	0.288
14. G. Ga.*....	10	69	100/ 68	44	M. S.	Dig.	+	0.872	+0.210 −0.191	0.618	+0.228 −0.217	0.254	+0.020 −0.029	0.056	+0.031 −0.026	0.198	+0.027 −0.035	0.290
15. M. St.	6	55	125/ 90	34	M. S.	Dig.	+	1.079	+0.478 −0.236	0.749	+0.467 −0.231	0.330	+0.011 −0.016	0.069	+0.012 −0.021	0.261	+0.022 −0.022	0.332
16. A. Wi.	6	46	160/100	50	My. F.	0	+	1.295	+0.277 −0.425	0.940	+0.272 −0.448	0.355	+0.015 −0.021	0.091	+0.012 −0.011	0.264	+0.007 −0.010	0.352

rate the phases of systole in normal persons compare with those obtained from the experimental observations of Wiggers and Katz, and that the changes in their duration follow the same laws.

DURATION OF SYSTOLE AND ITS PHASES IN AURICULAR FIBRILLATION

Comparison with Normal.—The data of sixteen series of observations on fifteen patients with auricular fibrillation are tabulated in Table 2. As this table shows, the patients were adults varying in age from 30 to 72 years (Column V), with blood pressures (maximum systolic—minimum diastolic) ranging from: systolic, 210, diastolic, 120; to systolic, 100; diastolic, 68 (Column IV). This series included seven cases with an associated myocardial fibrosis or so-called chronic myocarditis (*My.F.*) and eight with an associated mitral valvulitis (*M.S.*) (Column VI). Seven of the patients had not received any of the digitalis group of drugs (indicated by *O* in Column VII) while nine were "digitalized" to a variable degree when the records were obtained (*Dig.* in Column VII). Two of the latter had received some quinidin sulphate in addition (*Quin.* in Column VII). Three of the patients showed no evidence of cardiac failure at the time the record was taken (indicated by — in Column VIII), seven had signs of partial or moderate cardiac failure (± and + in Column VIII), and the other six exhibited evidence of marked failure (++ and +++ in Column VIII).

This table is also arranged according to the duration of the average cardiac cycle (Column IX). It gives a range of cycle lengths varying from 0.172 of a second in Case 1, to 1.72 of a second in Case 16, with a variation in predominant rate ranging from 186 to forty-six beats per minute (Column III). A careful analysis of this table shows that, as in the normal controls, the average diastole (Column X) lengthens with a lengthening of the cycle (Column IX), but not proportionately, the disproportion being due to the simultaneous lengthening of the average total systole (Column XI). Again as in normal cases, the duration of the average isometric contraction period (Column XII) varies independently of the other phases and of the predominant rate, whereas the average systolic ejection phase (Column XIII) in general changes directly with the cycle length and largely determines the duration of total systole.

A comparison of this table with Table 1 brings out some further interesting facts. Not only is the range of cycle lengths greater than normal in the series of auricular fibrillation cases, but the deviation from the average in a single case is also greater. This is also true of the duration of diastole and the isometric and ejection phases. Total systole, although deviating but little more from the average than normal, is surprisingly constant in a person with fibrillation, considering the greater variation of previous diastole. For example, Case 5, Table 2,

shows that with a variation of plus 0.113 and minus 0.119 of a second from the average cycle length (Column IX) and of plus 0.106 and minus 0.118 from the average diastole (Column X), the isometric contraction phase deviates from the average by only plus 0.057 and minus 0.021 of a second (Column XII), the systolic ejection by plus 0.021 and minus 0.049 of a second (Column XIII), and the total systole by plus 0.026 and minus 0.023 of a second.

Shortening of Systole and Its Ejection in Auricular Fibrillation.—A like comparison of averages shows the average isometric periods to be slightly longer in persons with auricular fibrillation than in normal persons (compare Column XII, Table 2, with Column VII, Table 1). Much more striking is the fact that the average total systoles and particularly the average ejection phases are shorter than normal at corre-

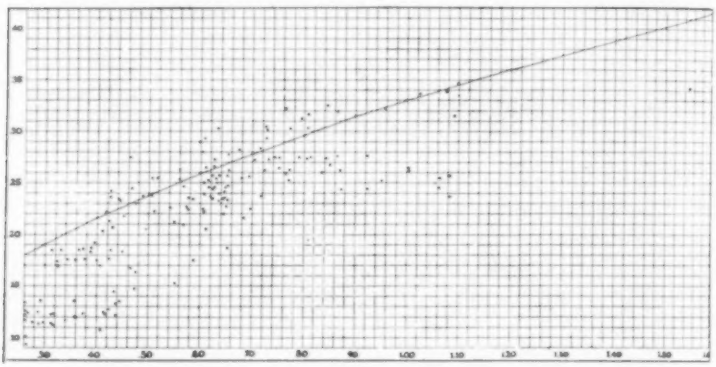

Fig. 3.—Plot showing the relation of total systole to corresponding cycle length in sixteen series of observations in fifteen cases of clinical fibrillation of the auricles, and related to curve drawn from the formula $S = 0.31 \sqrt{C}$.

sponding rates (compare Column XI and Column XIII, Table 2, with Column VI and Column VIII, Table 1).

This relative shortening is shown in another way, namely, by comparing the average ejection phase with *S* calculated (as pointed out above) for the corresponding average cycle length which is given in Column XIV. A little computation shows the average ejection phase in auricular fibrillation is from 0.019 to 0.092 of a second shorter than *S*, the average difference being 0.07 of a second. This is a considerably greater shortening than obtains in the normal series, the difference in the latter being, on the average only 0.028 of a second (as already mentioned). That this shortening of systole holds not only for average beats but also for individual beats is shown by plotting all systoles according to cycle length (Fig. 3). It is obvious that the individual

systoles in this figure are shorter and are closer to the line of calculated "systole"—cycle ratios (computed from the formula $S = 0.31\sqrt{C}$) than in Figure 2, the plot of the normal cases. Similar plotting of all the ejection phases showed an even greater difference between normal and fibrillation records.

What is the cause of this shortening? A survey of the variables given in Table 2 demonstrates that the shortening of ejection is unrelated to most of them. It is not related to the age of the patient, to the height of the blood pressure nor to the associated cardiac condition. It occurs in like degree in patients who have been "digitalized" and those who have not. The only condition that seems to modify it is the degree of cardiac failure.

Relation of Cardiac Failure to Duration of Systole and Ejection in Auricular Fibrillation—Anticipated Results.—It is apparent that cardiac failure increases the venous pressure because a relatively greater volume of blood is retained on the venous side—and with this the arterial pressure may be unchanged or even relatively reduced. We may anticipate then, *a priori*, that the increase in venous pressure and the lowering of the arterial pressure, when present, together with the slower rate of contraction of the diseased or fatigued heart, would lengthen the systole and its phases, and that this lengthening would vary directly with the degree of cardiac failure.

Actual Results.—Contrary to our expectations, and much to our surprise, the actual results (as shown above) are just the reverse. The duration of ejection seems to be inversely proportional to the degree of cardiac failure; that is, the length of systole, and particularly ejection, varies on the whole inversely with the degree of failure. For example, cases with no evidence of cardiac failure, Cases 3, 5 and 11, of Table 2, show a difference between calculated *S* and the average ejection of 0.019, 0.034 and 0.053 of a second, respectively (Column XIV minus Column XIII), an average difference of 0.035 of a second; while cases with marked cardiac failure, Cases 1, 2, 4, 6, 12 and 16, have respectively a difference of 0.09, 0.067, 0.064, 0.066, 0.085 and 0.088 of a second, or an average difference (0.076 of a second) more than twice that of the preceding cases. The cases with partial failure, Cases 7, 8, 9, 10, 13, 14 and 15 have differences between the other two, the differences being respectively 0.036, 0.063, 0.074, 0.067, 0.058, 0.092 and 0.061 of a second, an average difference of 0.064 of a second.

Discussion.—How can this discrepancy between anticipated and actual results be accounted for? Several explanations may be hazarded. For instance, an alteration in the blood chemistry associated with a deficient circulation might so change the condition of the heart as to make it contract for a shorter interval. Again, the pathologic condition

of the myocardium might alter its response to the progressive increase in venous pressure. Thus, we may suppose that the increase in venous pressure which in the early stages of failure is a compensatory mechanism becomes a detrimental factor as failure progresses, for we know that the inefficient (exhausted) heart fails to respond to the progressive increase of venous pressure and does not empty its contents completely.[11] Perhaps the duration of ejection reverses in a similar manner. There is, however, still another possible explanation.

Relation of Duration of Systole and Its Ejection to the Absence of Synergic Auricular Contraction in Fibrillation of the Auricles.—It is possible that this discrepancy between anticipated and actual results is peculiar to auricular fibrillation and does not occur when the mechanism is normal. Auricular fibrillation is characterized among other things by an absence of synergic auricular contractions, and this may be the cause of the shortening of ejection. Auricular systole has been found to contribute a variable but measurable amount of blood to the ventricles. Wiggers and Katz,[2] for example, recently found the auricular contribution to vary from 18 per cent. to 60 per cent. of the total filling in normal dogs. In auricular fibrillation the absence of this portion of the contribution and the consequent lessened filling would cause a relative shortening of systole and its ejection phase because of the relatively lower initial tension.

The validity of this hypothesis can best be tested in man in cases of paroxysmal auricular fibrillation. For in this condition there is a spontaneous alteration of mechanism within a short period of time which permits a comparison of the duration of systole and its ejection phase during both mechanisms in a single person under otherwise practically constant conditions. The patient in Case 2 of Table 2 happened to be such a person. In this patient auricular fibrillation would develop spontaneously, last a variable time (a few hours to several days) and then spontaneously revert to a normal mechanism. Fortunately for us, the heart rate remained rapid throughout, so that the changes in the duration of systole and its ejection phase, which were found, were not due to a change in heart rate. They could, therefore, be attributed to the absence of synergic auricular contractions. The paroxysms occurred many times during her stay in the hospital and even while she was receiving large quantities of digitalis, as well as during the time she was receiving quinidin sulphate. The patient had signs of marked cardiac failure and died a short time after the records were taken. The diagnosis of paroxysmal auricular fibrillation was of course confirmed

11. Wiggers, C. J., and Katz, L. N.: Am. J. Physiol. **58**:439, 1922. Patterson, S. W., and Starling, E. H.: J. Physiol. **48**:357, 1914; Patterson, Piper, and Starling: J. Physiol. **48**:465, 1914.

electrocardiographically. Figure 4 presents the electrocardiogram, Lead II, taken during auricular fibrillation and Figure 5 during normal mechanism. The two sets of observations were taken two days apart. Twenty-two beats were measured on each occasion.

The average durations (and deviation from the average) are tabulated in Table 3. Analysis of this table shows a slightly more rapid predominant rate during fibrillation than when the mechanism was normal. Ejection and systole shorten more than can be accounted for by

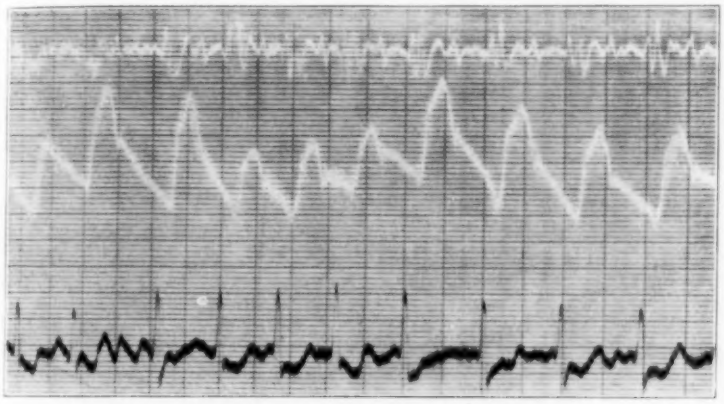

Fig. 4.—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II, (bottom curve) of a case of paroxysmal auricular fibrillation during a period of fibrillation.

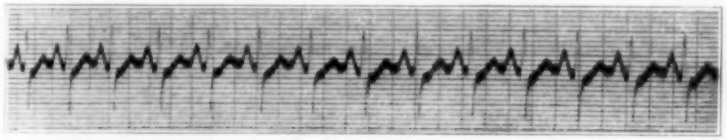

Fig. 5.—Electrocardiogram, Lead II, from patient illustrated in Figure 4, during normal mechanism.

this slight change in rate. According to the calculated *S*, "systole" should be 0.015 of a second shorter during the fibrillation than during the period of normal mechanism, whereas in reality the shortening of the average ejection is 0.043 of a second and that of the average total systole is 0.051 of a second. When the auricular contractions are present, the average ejection phase is 0.039 of a second less than the corresponding calculated *S*, while the difference is almost twice as great (0.067 of a second) when the synergic auricular contractions are absent. If the change in duration of ejection is compared with the change in

the length of the preceding diastole, the discrepancy is even greater, as is also the case when a tabulation of all the beats is analyzed (Fig. 3).

This case, therefore, shows that the absence of synergic auricular contraction causes in itself a relative shortening of systole and ejection. Indeed the progressive shortening with cardiac failure found in this series (Table 2) may be attributed to the greater susceptibility of the inefficient heart to slight changes in initial tension. Thus, on this assumption it can be argued that the decrease in filling produced by the absence of auricular contraction elicits a relatively greater response (shortening of ejection time) in the failing heart than in the efficient one; and that this response (shortening) is proportional to the degree of cardiac failure. At the present time, this appears to be the most logical explanation. Observations of other clinical conditions and on

TABLE 3.—*Average Duration of Systole and Deviations from the Average in a Case of Paroxysmal Auricular Fibrillation*

I	II	III	IV	V	VI	VII
Cardiac Mechanism	Predominant Rate	Duration of Cycle	Duration of Preceding Diastole	Duration of Total Systole	Duration of Systolic Ejection	Duration of Systole as Anticipated From Formula $S = 0.31\sqrt{C}$
Auricular fibrillation.....	151	+0.155 0.397 sec. −0.076	+0.180 0.222 sec. −0.075	+0.013 0.175 sec. −0.024	+0.017 0.128 sec. −0.021	0.196 sec.
Normal.....	130	+0.018 0.460 sec. −0.016	+0.025 0.234 sec. −0.010	+0.012 0.226 sec. −0.015	+0.014 0.171 sec. −0.010	0.210 sec.
Difference.....	21	0.063 sec.	0.012 sec.	0.051 sec.	0.043 sec.	0.015 sec.

animals are, however, contemplated to further test the validity of this hypothesis.

THE DYNAMIC INFLUENCE OF THE CONSTANTLY CHANGING CYCLE LENGTH IN AURICULAR FIBRILLATION

Effect on the Duration of Systole and Its Phases in Successive Beats.—Changing heart rate in normal animals has been found to alter not only the duration of systole and its phases, but also the systolic discharge and velocity of ejection.[12] It is therefore interesting to see if this is also true in man. The constantly changing rate in auricular fibrillation gives an opportunity to determine this.

An analysis of our results demonstrates that the duration of the systolic phases alters from beat to beat with changes in cycle length. Indeed the response is practically the same regardless of the condition

12. Henderson, Y., and Associates: Am. J. Physiol. **16**:325, 1906; ibid. **31**: 288; 352, 1913. Straub, H.: Deutsch. Arch. f. klin. Med. **115**:531, 1914; ibid. **118**:214, 1915. Also Foonote 11.

of the heart or circulation. In general a lengthening of diastole causes an almost proportional lengthening of the following ejection period and an almost proportional shortening of the isometric period, whereas a shortening of diastole has the opposite effect. Total systole varies in the same direction as the ejection phase, but because of the opposite

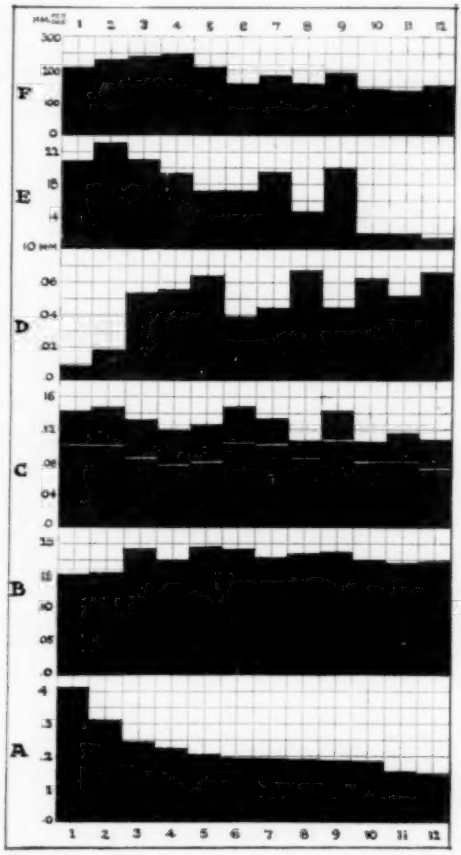

Fig. 6.—Relation of the dynamics of systole to diastole.

change in the isometric period, to a lesser degree. There are, however, many exceptions to all of these relationships. A typical Case is graphically illustrated in Figure 6 compiled from Case 10, Table 2. The twelve beats of this series are arranged according to the duration of diastole, starting with the longest and ending with the shortest (Fig. 6, *A*). Figure 6, *B* represents the duration of the corresponding suc-

ceeding total systoles. These shorten only slightly with the shortening of diastole and show many independent variations. Figure 6, *C* represents the duration of the ejection phases. These vary more than the total systole and follow the duration of the preceding diastole more closely but with occasional exceptions. Figure 6, *D* indicates the duration of the isometric contraction phases. This period varies with the duration of the preceding diastole with only few exceptions, but in the opposite direction; it lengthens as the diastole shortens. This effect of the diastole on the isometric period accounts for the relatively more constant duration of total systole, for the latter is from this point of view the sum of its phases, and these vary in opposite directions.

These findings confirm and extend those of Weitz,[13] who obtained similar results in a smaller series of clinical cardiac arrhythmias by a different method, but which is not free from criticism.

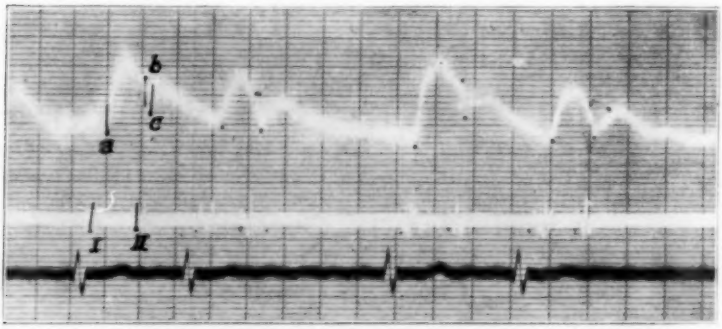

Fig. 7.—Simultaneous record of heart sounds (middle curve), subclavian arterial pulse (upper curve) and electrocardiogram, Lead II (bottom curve) from a case of auricular fibrillation.

The Effect of Changing Cycle Length on the Size of the Pulse in Successive Beats.—In studying successive beats in the central pulse by optical means (such as Figs. 4, 7 and 8), we find that the changes are the same as in the radial pulse. As a rule, large beats succeed long diastolic pauses, and small beats follow short intervals. At times, however, small beats succeed long pauses, and vice versa. In general, the size of each beat varies directly with the length of the preceding diastole but not proportionately. There is a greater variability in height in beats with short preceding diastoles. Slight differences in diastole cause greater changes in height in these beats than in those occurring after longer pauses.

13. Weitz, W.: Deutsch. Arch. f. klin. Med. **127**:325, 1918.

Figure 6 illustrates these findings graphically. Figure 6, *E* represents the height of the individual pulse beats (in millimeters) in the case already referred to. When this is compared with the duration of the preceding diastole (Fig. 6, *A*) we find that the height of the beat on the whole decreases as the diastole shortens, although there are many deviations, and that this shortening is proportionately greater in the beats with the shorter diastoles.

Do these changes in pulse size indicate like changes in systolic discharge? According to Frank [14] the arterial pressure (and with it the pulse) is the result of two variable factors—the rate of ejection from the ventricle and the peripheral flow from the arterial system. The peak of the pulse curve marks the point at which the two are equal. It also marks the end of the maximum ejection phase and the beginning

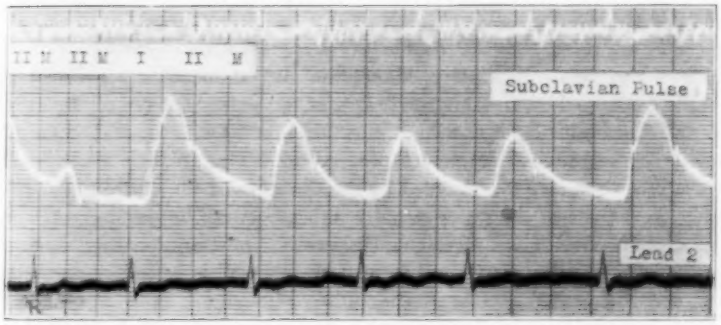

Fig. 8.—Simultaneous record of heart sounds (top curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) from a case of auricular fibrillation. *M*, diastolic murmur; I and II first and second heart sounds, respectively.

of reduced ejection (Wiggers [1]). The size of the pulse, therefore, actually indicates only the amount of blood ejected during the maximum ejection phase. It gives no indication of the output during reduced ejection, because the latter occurs at the beginning of the descending limb of the pulse (catacrotus). However, it has been found that in animals the output during maximum ejection not only constitutes the major portion of the total systolic discharge, but it also varies more or less proportionately with the latter under a large variety of conditions (Wiggers and Katz [2]). The changes in pulse size are therefore interpreted as indicating, to a fair degree of accuracy, the variations in relative systolic discharge.

14. Frank, O.: Ztschr. f. Biol. **46**:478, 1905.

This method of estimating the systolic discharge was used only in studying consecutive beats, because only under such circumstances can we maintain a comparative uniformity of the mechanical factors involved in taking the record, that is, the pressure applied over the subclavian artery and the condition of the recording capsule. The modification which the elasticity coefficient of the aorta and subclavian artery produce is so slight that for estimations such as ours it plays an insignificant rôle. This is probably the simplest clinical method available at present for such determinations in cardiac irregularities. It is more accurate than the usual methods utilizing pulse pressure, in that it is obtained optically. The gas methods used by Zuntz, Plesch, Krogh and others [15] cannot be used in cases of auricular fibrillation because of the great variability in cycle length and pulse size.

We, there, interpret these findings as indicating that changes in the systolic discharge occur in auricular fibrillation, partly as a result of the varying cycle length, but also because of other factors.

The Effect of the Altering Cycle Length on the Velocity of Ejection.—The relative velocity of ejection in consecutive beats can be readily obtained by dividing the height of the pulse beat (in millimeters) by the duration of the maximum ejection phase (in seconds), the result being expressed in millimeters per second. This gives a truer result than when the height is divided by the duration of the entire ejection in that the height of the pulse actually indicates only the discharge during maximum ejection, as already mentioned. The duration of the maximum ejection phase is given by the time interval between the beginning of the rise and the peak of the pulse. In Figure 6, *c*, the ejection phases are subdivided into the two periods by white lines. The maximum ejection is the portion to the white line; the reduced ejection is the part above.

When the velocity of ejection was determined in this way in successive beats, it was found that almost without exception it varied directly with the size of the pulse, and inversely with the duration of the isometric period. This is graphically shown for a typical case in Figure 6 when one compares the graph of ejection *rate* in this case (Fig. 6, *F*) with the height of the beat (Fig. 6, *E*) and with the duration of the isometric period (Fig. 6, *D*). This indicates, in the first place, that in auricular fibrillation in man, as in animals in whom some arrhythmia is present, the amount of the systolic output varies from beat to beat, not only because of the changing duration of ejection but also because of a change in the velocity of ejection. In the second place, it shows, so we believe, that the rapidity of ventricular

15. Zuntz, E.: Ztschr. f. klin. Med. **74**:347, 1912. Plesch, J.: Zentralbl. f. Physiol. **26**:89, 1912. Krogh, A., and Associates: Skand. Arch. f. Physiol. **27**:100, 126 and 227, 1912.

contraction is the important factor in determining the duration of the isometric period; or conversely, that the rapidity of ventricular contraction is fairly accurately given, within limits, by the duration of the isometric period. This last agrees with the observation of Wiggers [2] that the duration of the isometric contraction period is determined by the initial tension because, so we infer, it alters the rapidity of ventricular contraction.

Discussion.—The effects of changing cycle length in cases of auricular fibrillation are in close agreement with recent results obtained on experimental animals, and they follow the same laws. The duration of systole and its phases, the height of the beat and the rapidity of contraction all depend, in the first place, on the initial tension and diastolic volume of the ventricle, and in the second place, on the condition of the myocardium. The predominant influence of the duration of the preceding diastole results from its effect on these two factors; by modifying the duration of filling it determines the initial tension and diastolic volume of the ventricle, and by modifying the period of rest it determines the condition of the myocardium. The changes in arterial resistance (diastolic blood pressure) that result from the variations in the duration of diastole may play some part, particularly in hypodynamic hearts as Einthoven and Korteweg [16] held, but this, we believe, is of relatively minor importance.

The occasional deviation from this influence of diastole can be explained by the action of other influences on the initial tension and condition of the myocardium, as in the experimental and normal cases. These influences include varying tonus of the cardiac nerves and variations in venous return such as result from respiration because of dyspnea. When failure is present, and it is here that the exceptions are more frequent, we may add the inotropic effect of varying oxygen and carbon dioxid tensions of the blood and the influence of changing chemistry of the heart fluids. The deviation may be the result of imperfect or delayed relaxation as suggested by Lewis,[17] or it may, according to Hering's hypothesis,[18] result from the varying quantities of myocardial fibrils in contraction.

Whatever the cause may be, the results confirm the fact that the response of the ventricle in auricular fibrillation, as in normal persons and experimental animals, is modified by other factors than the duration of the preceding diastole. Although the duration of the diastole is the most important, it is not the only influence concerned in the dynamics of ventricular systole.

16. Einthoven, W., and Korteweg, A. J.: Heart **6**:107, 1915-1917.
17. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1920, p. 385.
18. Hering, H. E.: München. med. Wchnschr. **55**:931, 1908.

Our results show, furthermore, how nicely the ventricle adapts itself to changing dynamics, and our study enables us to formulate a conception of this adapting mechanism.

SUMMARY

1. A study of optically recorded heart sounds and the subclavian pulse was made in a series of fifteen normal persons and in a series of fifteen persons with auricular fibrillation. A method is given for determining the duration of systole and its phases from these records.

2. As a result of the study of the normal series, which includes almost 500 measurements, we find that with a variation in heart rate from 100 to fifty-four beats per minute, the isometric contraction phase varies from 0.024 to 0.089 of a second, the ejection phase from 0.22 to 0.298 of a second and the total systole from 0.262 to 0.374 of a second. The isometric period varies independent of the rate and of the duration of the other phases, whereas ejection and total systole are determined chiefly but not entirely by the duration of the preceding diastole. The duration of total systole is determined largely by the duration of ejection.

The formula $S = K/\overline{C}$ was tested and found to be of value in indicating the influence of cycle length on the duration of ejection.

The results in the normal series are in accord with the results of Lombard and Cope and more closely with those of Wiggers and Clough. They also agree with the experimental observations of Wiggers and Katz and follow the same laws.

3. As a result of the study of sixteen series of observations on fifteen cases with auricular fibrillation, which includes about 1,500 measurements, we find a greater variation in the cycle length both in the entire series and in individual cases than occurs in the normal series, and with this there is a greater variability in the duration of systole and its phases. With a predominant heart rate ranging from 186 to forty-six beats per minute, the isometric contraction period varies from 0.006 to 0.152 of a second, the systolic ejection phase from 0.055 to 0.293 of a second and the total systole from 0.096 to 0.37 of a second.

On comparing the average durations in the two series we find that in auricular fibrillation, as in the normal cases, the duration of the average systole and its ejection phase is determined chiefly, but not entirely, by the duration of the corresponding average diastole.

The isometric period is on the whole slightly longer than normal, but like the isometric period of the normal person, it bears no relation to the predominant rate or the average duration of the other phases.

Much more striking is the fact that the average total systole, and more particularly the average ejection phase, is shorter than normal at corresponding rates. This relative shortening of total systole and

its ejection phase is also found when the plots of all the beats in the two series are compared. It is not related to the age, to the blood pressure, to the etiology of the fibrillation or to the amount or type of therapy received, but apparently only to the degree of cardiac failure. Contrary to our expectations, the length of systole and its ejection phase is not directly but in a general way more or less inversely proportional to the degree of failure.

In attempting to explain this discrepancy, we studied a case of paroxysmal auricular fibrillation during both mechanisms, and found that under otherwise practically constant conditions the duration of systole and ejection was relatively shorter during a period of auricular fibrillation than during the normal mechanism. We attribute this shortening to the absence of synergic auricular contractions in auricular fibrillation. On this assumption the relative shortening is due to the absence of the auricular contribution to ventricular filling. The relation of this shortening to the degree of failure is explained by assuming that the response of the ventricle to this relatively smaller filling is increased in the failing heart more or less proportionately to the degree of failure. Other mechanisms may operate, but at the present time this one seems the most logical.

4. The constantly changing cycle length in cases with auricular fibrillation permitted the study of its effect on the dynamics of systole.

The relative systolic output during the maximum ejection phase is indicated by the height of successive beats in the optically recorded subclavian pulse, and this height divided by the duration of the *maximum ejection* phase gives the relative velocity of ejection.

In any person with auricular fibrillation, we find that the dynamics of successive ventricular systoles are primarily but not entirely determined by the duration of the preceding diastole. In general, a change in the duration of diastole causes a like change in the succeeding systolic discharge (as indicated by the height of the pulse), in the duration of systole, and in the duration and velocity of ejection, but produces an opposite change in the duration of the isometric period. The more constant duration of total systole in a single case results from the opposite effect of diastole on the durations of the systolic phases.

The occasional deviations from the influence of diastole is explained, as in experimental animals, by the effect of alterations in venous return, in tonus of the cardiac nerves, etc. In view of the pathologic condition of the heart muscle and the failing circulation in some cases, other additional factors probably operate. The alterations in the tension of blood gases, changing chemistry of the heart fluids, imperfect or delayed relaxation (as suggested by Lewis) or other deviations in

ventricular filling, and variations in the number of contracting ventricular fibrils (according to Hering's hypothesis) are suggested as possible causes.

In addition, this study shows that the variations in systolic discharge are the product of two other variables, namely, the rate of ejection and its duration.

It shows further that with certain reservations the duration of the isometric period is an index of the rapidity of ventricular contraction.

5. We conclude from these observations that in man, as in animals, the changes in the dynamics of ventricular systole occur primarily as a result of changes in two factors, the one physiologic, that is, the condition of the myocardium, and the other physical, that is, the tension and volume of the ventricle at the beginning of systole.

LAMBLIA (GIARDIA) INFECTION ASSOCIATED WITH CHOLECYSTITIS

REPORT OF A CASE TREATED WITH NEO-ARSPHENAMIN *

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INCIDENCE

It is now generally agreed that *Lamblia* infection of the intestinal tract is not as rare as it was thought to be before the World War. Surveys in America and in Europe indicate that lambliasis is possibly the second most common of the protozoal infections, being surpassed in frequency only by endamebiasis (Hegner and Payne;[1] Fantham and Porter;[2] Kofoid, Kornhauser and Plate[3]). In children, at least in those in institutions, the infection is even still more common than in adults (Maxcy[4]).

DIAGNOSIS

Until recently the diagnosis of *Lamblia* infection could be made only by an examination of the stools. With the increased employment of the intestinal (duodenal) tube, the diagnosis can also be established simply by direct microscopy of the aspirated duodenal contents. Since the active, flagellate form of the parasite is found in the duodenum, it is not necessary to employ the differential staining methods required to identify the encysted forms in the stools. Whether the tube method is more accurate than the stool method in the sense of revealing a greater number of infections, has not yet been established. Owing to their lightness and to the concentration of the protozoa in the upper intestine, one might expect the tube method of diagnosis to be clinically effective. This is not the case with a nonprotozoal inhabitant of the upper intestine, namely the hookworm, as I found that the aspiration of uncinaria ova for the purpose of diagnosis—even in heavily infected carriers—occurred far too seldom to be of any value as a diagnostic measure. In the case of *Lamblia*, therefore, special comparative studies of this nature would be welcome.

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* Read at the Twenty-Sixth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 1, 1923.

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4. Maxcy, K. F.: Giardia (Lamblia) Intestinalis, a Common Protozoan Parasite of Children, Bull. Johns Hopkins Hosp. **32**:166-170, 1921.

More and more cases of lambliasis, however, are now being recognized by duodenal aspiration. In most cases this has been an accidental finding in the course of bile drainages for other—diagnostic or therapeutic—purposes. The original publication of M. W. Lyon,[5] who found *Giardia* in the duodenal contents of two patients at the Walter Reed Hospital, was followed by similar reports from B. B. V. Lyon,[6] Smithies,[7] Simon,[8] Hollander,[9] and Knighton [10] in this country, and by Boyd [11] in Canada. In the author's case also the diagnosis was made by this method.

PATHOGENICITY

The most common clinical condition associated with *Lamblia* infection is an enterocolitis. It is now recognized that diarrhea need not invariably occur in the presence of infestation with this parasite. In this respect one is reminded of the growth of our knowledge concerning *Strongyloides intestinalis,* which was at first thought to be directly associated with Cochin-China diarrhea. When diarrhea is not present, the enterocolitis of lambliasis may be expressed by other symptoms such as constipation, irregular bowel action, colic, and the presence of mucus in the feces. The facts pointing most strongly to the pathogenic rôle of *Lamblia* has been well presented by Fantham and Porter, who found postmortem, destructive changes in the intestinal epithelial cells, and by Fairise and Jannin [12] as well as by Kofoid and Christansen,[13] who found the parasite embedded in the deeper layers of the intestinal mucosa.

There is, however, another aspect of the pathogenicity of *Lamblia* infection which is, or at least might well be, of great clinical interest,

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9. Hollander, E.: Personal Communication.

10. Knighton, J. E.: Lamblia Intestinalis with Report of Cases, South. M. J. **15**:457-458, 1922.

11. Boyd, W.: The Detection of Lamblia (Giardia) Intestinalis by Means of the Intestinal Tube, Canad. M. A. J. **11**:658-660, 1921.

12. Fairise, C., and Jannin, L.: Dysenterie chronique à Lamblia, étude parasitologique et anatomo-pathologique, Arch. d. med. expér. et d'anat.-path. **25**:525-551, 1913.

13. Kofoid, C. A., and Christansen, E. B.: On Giardia microti sp. nov., from the Meadow Mouse, Univ. Calif. Publ. Zool. **16**:23-29, 1915.

and that is the tendency of the organism to invade the bile passages and the gallbladder. Six years ago, Smithies reported the actual presence of *Lamblia* in an infected gallbladder removed at operation. Since that time several other authors have made incidental mention of associated symptoms strongly pointing to gallbladder involvement (B. B. V. Lyon,[6] Simon,[8] Hollander,[9] Knighton [10]). I shall focus attention further on the question of *Lamblia* cholecystitis.

THERAPY

Until recently lambliasis, at least in the severe form, has been regarded by many discriminating workers as being practically incurable. The large number of therapeutic procedures that have been tried and found wanting has often been recorded. Dobell and Low,[14] in a well controlled case, failed completely with bismuth salicylate, beta-naphthol, methylene blue, turpentine, and guaiacol carbonate. Cade and Hollande [15] were similarly disappointed with emetin hydrochlorid given hypodermatically, emetin bismuth iodid by mouth, salicylic acid, hydrochloric acid, quinin sulphate, picric acid, and arsphenamin by mouth. Simon failed to cure by transduodenal lavage with Jutte's hypertonic saline solution, and I failed with similar lavage with strongly acidulated saline. In this connection, as in all parasitic infections, it should be borne in mind that the criteria of cure are to be strictly followed, it having been shown, particularly by Dobell and Low, and by Porter,[16] that a long period of observation is absolutely necessary to insure a safe verdict as to the results of therapy.

It was not until 1917 that any real hope for the successful treatment of giardiasis was forthcoming. In that year, Yakimoff [17] and his co-workers showed definitely that arsphenamin was capable of killing *Lamblia*. These workers experimented with mice and checked their results carefully by postmortem examination. Similar findings were obtained subsequently in this country by Kofoid and his associates, who succeeded in curing *Lamblia*-infested rats by administering massive doses of neo-arsphenamin. In 1918, Cade and Hollande and Goiffon and Roux [18] treated human giardiasis with arsphenamin and neo-arsphenamin but obtained indifferent results. In all probability, as

14. Dobell, C., and Low, G. C.: A Note on the Treatment of Lamblia Infections, Lancet **2**:1053, 1916.
15. Cade, A., and Hollande, A. C.: L'Entérite à "Giardia (Lamblia) Intestinalis," Arch. d. mal. d. l'app. digestif. **10**:193-222, 1919.
16. Porter, A.: An Enumerative Study of the Cysts of Giardia (Lamblia) Intestinalis in Human Feces, Lancet **1**:1166-1169, 1916.
17. Yakimoff, W. L.; Wassilevski, W. J., and Zwietkoff, N. A.: Sur la chimiothérapie de la lambliose, Scéances et mém. Soc. Biol. **80**:506-507, 1917.
18. Goiffon, R., and Roux, J. C.: Les entérites à Lamblia, Arch. d. mal. de l'app. digestif. **9**:601-615, 1918.

is now apparent, their initial dosage was too small. In 1920, however, Carr and Chandler [19] reported the cure of a case by a series of four intravenous injections of neo-arsphenamin 0.6 gm. each. Dr. Chandler writes to me that this case has remained negative for two and a half years, as proved by repeated stool examinations. It may therefore be regarded as the first carefully controlled cure of this disease on record.

In a further communication, Dr. Chandler says:

> The successful employment of neo-arsphenamin in the treatment of intestinal protozoal diseases depends entirely on getting enough of this product, or whatever modification of it reaches the intestine, into the intestin at one time to kill the organisms present. For Giardia we have found that in patients 25 to 30 years of age who do not have an intensive intestinal ulceration three injections of 0.6 gm. at five day intervals are sufficient to take care of the infection. However, if the secretory function of the gut is impaired through age or extensive ulceration, a larger dose, at least a larger initial dose—usually 0.9 gm.—is required to accomplish the desired results. . . . If in the treatment of intestinal protozoal diseases the initial dose is small (0.3 gm. or less) the invading organism appears to develop a tolerance to neo-arsphenamin to such an extent that later larger doses often fail to destroy it.

The last sentence is of particular significance and might serve to explain many of the failures described in the literature. Since the publication of Carr and Chandler's case, two communications reporting treatment with neo-arsphenamin have appeared, one by Reverdin and Chomé,[20] the other by Simon.[8] The Swiss authors mention one case which they treated with five injections (dose not stated) at three day intervals and which remained negative for the nine months to date of publication. Simon administered the drug to five patients, four times intravenously, and once through the duodenal tube. Unfortunately, the dose—with one exception—was not stated, and the observation of results after treatment was apparently not exhaustive. The immediate effects, however, were quite satisfactory.

The question now naturally arises, In what way is arsphenamin or its cogeners effective in ridding the organism of intestinal protozoa? A survey of the literature bearing on arsphenamin and its behavior in and excretion from the body has proved most fascinating. Soon after the introduction of arsphenamin by Ehrlich in 1910, studies began to appear on the fate of the drug in the body. Such workers as Fischer and Hoppe [21] (1910) and Bornstein [22] (1911) succeeded in demon-

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19. Carr, E. I., and Chandler, W. L.: Successful Treatment of Giardiasis in Man with Neo-Arsphenamin, J. A. M. A. **74**:1444-1445, (May 22) 1920.

20. Reverdin, A., and Chomé, E.: Lamblia intestinalis, Rev. méd. de la Suisse Romande **42**:118-119, 1922.

21. Fischer, P., and Hoppe, J.: Das Verhalten d. Ehrlich-Hataschen Präparates im Menschlichen Körper, München. med. Wchnschr. **57**:1531-1532, 1920.

22. Bornstein, A.: Ueber das Schicksal des Salvarsans im Körper, Deutsch. med. Wchnschr. **37**:112-113, 1911.

strating that soon after its intravenous injection the arsphenamin leaves the blood and becomes deposited or fixed in certain natural depots of the body, such as the liver, kidneys and spleen. At this early date, the excretion of the arsenic was being actively studied in the urine, particularly by Abelin [23] (1911), but its excretion in the stools, though recognized even by the earliest workers, was not accorded sufficient attention. As far back as 1912, Ullmann [24] found from experiments in rabbits that not only do the liver, kidneys and spleen fix the arsenic, but that even a few minutes after its injection the drug arrives in the gastro-intestinal tract—probably in the blood vessels and glands thereof—where it is in part fixed and in part excreted through the intestinal secretions and dejecta, to be in turn partially reabsorbed through the portal circulation.

In 1913, Frenkel-Heiden and Navassart [25] showed by a comparative study of the urine and feces that from two to ten times as much arsphenamin is excreted by the intestine as by the kidneys. That arsenic is excreted by the stomach was shown as early as 1910 by Jeanselme, Bongrand and Chevalier,[26] who found about 0.01 gm. arsenic in the vomitus of a patient who had received 0.6 gm. arsphenamin five to eight hours previously.

In 1914, Stuehmer [27] confirmed the presence of arsenic in the stomach and small intestine and was apparently the first to attempt to demonstrate its presence in the bile. His results proved inconclusive, but as he likewise failed to find arsenic in the stool, it seems fair to conclude that his methods were perhaps at fault.

Probably the first to show that arsenic was actually excreted through the bile was Pomaret [28] (1920), who injected 0.3 gm. neo-arsphenamin into a dog, fixed a cannula in the common bile duct, and recovered within one hour arsenic corresponding to more than 0.01 gm. of arsphenamin. Incidentally, the amount thus excreted through the biliary system was found to be greater than that excreted by the kidney in the same interval.

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23. Abelin, J.: Beginn u. Dauer der Ausscheidung des Salvarsans nach intravenöser Injektion, München. med. Wchnschr. **58**:1771-1773, 1911.

24. Ullmann, K.: Ueber Ausscheidungswerte u. Speicherungsverhältnisse nach Einfuhr von Salvarsan in der menschlich-tierischen Organismus, Arch. f. Dermat. u. Syph. **114**:511-570, 1912.

25. Krenkel-Heiden and Navassart: Ueber das Schicksal des Salvarsans im menschlichen Körper, Ztschr. f. exper. Path. **13**:531-542, 1913.

26. Jeanselme, E.; Bongrand, J. C., and Chevalier, P.: Sur le rhythme de l'élimination de l'arsenic après l'injection intramusculaire ou souscutanée de produits organo-arsenicaux solubles et en particulier d'hectine, Bull. et mém. méd. d. hôp. de Paris **30**:743-752, 1910, ser. 3.

27. Stuehmer, A.: Zur Topographie des Salvarsans und Neosalvarsans, Arch. f. Dermat. u. Syph. **120**:589-610, 1914.

28. Pomaret, M.: L'Elimination des arsénobenzols, La méd. **2**:123-125, 1920.

During the past year (1922), three important chemical studies have appeared in this country by Voegtlin and Thompson,[29] by Underhill and Davis,[30] and by Clausen and Jean,[31] all definitely showing that arsenic is excreted far more profusely by the gastro-intestinal tract than by the urinary system. These findings show that the same is true of arsenic that has already been experimentally demonstrated for mercury and other heavy metals, namely, that "the chief channel of elimination is by way of the bowel and relatively little of these substances can be made to pass out by way of the urine under any circumstances (Sansum[32])." The actual rate of excretion of arsenic into the intestinal tract varies with the different arsenicals, Voegtlin and Thompson having shown that it amounts, within the first twenty-four hours, to the surprising proportions of 33 per cent. of the dose injected in the case of neo-arsphenamin and 82 per cent. of the dose in the case of arsphenamin. The same authors have also found that the "bile contains considerable amounts of arsenic after the intravenous injection of arsphenamin and neo-arsphenamin." (Personal communication.)

At this point a few remarks as to the administration of arsphenamin by rectum may be in order. In several of the cases of lambliasis reported since the era of arsphenamin protozootherapy it was remarked that the intravenous mode of administration was refused by the patient. In the case I report the veins were so small as to cause unusual difficulty in consummating this form of treatment. In all such cases, as well as in children, it is quite possible that the drug may be exhibited successfully per rectum. Boyd and Joseph[33] (1918) were the first in this country to advocate this type of therapy. It has more recently been shown by Mehrtens[34] (1921) that when arsphenamin is administered by rectum in sufficiently large doses, arsenic is absorbed into the blood, that it persists there longer, and that larger quantities are eliminated in the urine (and presumably reexcreted into the intestine) than after the ordinary intravenous administration. To achieve this purpose, Mehrtens recommends a dosage of 4 gm. of neo-arsphenamin.

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29. Voegtlin, C., and Thompson, J. W.: Rate of Excretion of Arsenicals, a Factor Governing Toxicity and Parasiticidal Action, J. Pharmacol. & Exper. Therap. **22**:85-105, 1922.

30. Underhill, F. P., and Davis, S. H.: The Excretion of Arsenic After Serial Administration of Arsphenamin and Neo-Arsphenamin, Arch. Dermat. & Syph. **5**:40-50 (Jan.) 1922.

31. Clausen, S. W., and Jean, P. C.: Distribution and Excretion of Arsenic After Intravenous Administration of Arsphenamin in Children, Am. J. Syphilis **6**:556-567, 1922.

32. Sansum, W. D.: The Principles of Treatment in Mercuric Chlorid Poisoning. An Experimental Study, J. A. M. A. **70**:824-828 (March 23) 1918.

33. Boyd, A. S., and Joseph, M.: Intrarectal Administration of Arsphenamin, J. A. M. A. **71**:521-523 (Aug. 17) 1918.

34. Mehrtens, H. G.: Rectal Injection of Massive Doses of Neo-Arsphenamin, J. A. M. A. **76**:574-576 (Feb. 26) 1921.

SUMMARY AND CONCLUSION

1. Arsenic disappears from the blood soon after intravenous injection.

2. It is fixed in certain natural depots of the body, particularly in the digestive canal and the liver, and to a less extent, in the kidneys and spleen.

3. Arsenic excreted into the intestinal tract is in part eliminated through the feces, but is in part also reabsorbed through the portal circulation.

4. The liver excretes arsenic into the bile in relatively large quantities.

5. Arsphenamin administered by rectum in large enough doses probably behaves systemically in the same way as when given intravenously.

It follows from the foregoing that we have in arsphenamin or neo-arsphenamin therapy a precise and effective method of reaching susceptible protozoan parasites no matter how deeply they may invade the intestinal or biliary mucosa.

REPORT OF A CASE

History (April 20, 1922).—Miss L. M., aged 30, a trained nurse, referred by Dr. Ira Cohen, was born in Michigan, where she lived until she came to New York City in 1907. About twelve years ago she began to have pains in the right side of the abdomen, radiating to the groin, interfering when she walked, and becoming more marked before the menstrual periods. There was never actual prostration, nor was there any vomiting, abdominal rigidity or fever. The bowels moved habitually two or three times a day. More frequent and looser movements might have occurred at times, but the patient was not certain about this.

Seven years after the onset of these pains the patient was operated on, and a "clean" appendix was removed. While in bed following the operation, she experienced pains at the waist line with radiation to the back. Roentgenograms of the kidney region proved negative for calculi. The patient remained free from symptoms for a period of two years following the operation.

Three years ago the pains recurred, but they were located higher up than originally, extending under both rib margins and radiating to the back between the shoulder blades. The attacks generally took place at 9 or 10 p. m. As before, they showed a tendency to come on with the menses, except that for the past three months they had become practically constant.

During the past year there was increasing abdominal distention, especially after meals, and more marked on the right side. Recently the upper part of the abdomen had become so sensitive that the pressure of the corset or of any tight waist bands caused extreme discomfort. At no time had there been jaundice.

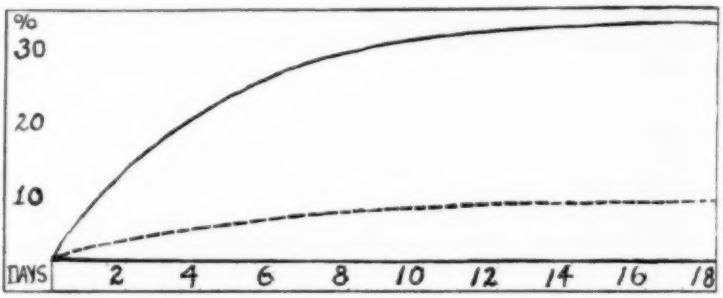
Examination.—This revealed a stocky young woman, 20 pounds (9.07 kg.) overweight, not acutely ill, who was organically sound except for a liver that was palpable about two fingerbreadths below the right costal margin and which was distinctly tender on pressure. There was no jaundice and no fever The urine was negative, except for an excess of indican.

Intubation of the stomach showed that it was empty when fasting. After an Ewald test breakfast free acid was absent; the total acidity was 17. Roentgen-ray examination of the digestive tract was negative as regards form and function, except that there was a persistent shallow filling defect on the outer (right) aspect of the duodenal cap.

Diagnosis.—In view of the history, the tenderness and enlargement of the liver, the achlorhydria and the defect in the duodenal cap corresponding to the region of the gallbladder, a diagnosis of subacute cholecystitis was made.

Treatment.—As there seemed no urgent indication for surgical intervention, routine medical treatment was instituted. On May 3, 1922, a duodenal tube was introduced for the purpose of effecting bile drainage. The sediment of the recovered fluid was found, on microscopic examination, to contain innumerable, actively motile flagellate organisms readily identified as *Lamblia intestinalis (Giardia enterica).*

In view of Simon's then recent report of an apparent cure of *Lamblia* infestation by a series of transduodenal flushes with Jutte's solution, a similar plan of therapy was decided on. From May 3 to May 11, inclusive, the patient received four flushes of 900 c.c. each of hypertonic saline (sodium sulphate and



Arsenic excretion (after arsphenamin injection) in urine and feces as percentage of the injected dose, showing the relatively greater excretion in the feces, the slow excretion after from eight to ten days, and that after two weeks about 50 per cent. of the arsenic is not yet excreted (after Clausen and Jean). The continuous line indicates the arsenic excretion in the feces; the broken line that in the urine.

sodium chlorid, 9 parts each per 1,000). As there was no apparent diminution in the number of flagellates present in the duodenal contents, it was decided to add hydrochloric acid to the flush solution in the hope of rendering the environment unfavorable to the parasites, it being commonly supposed that gastric anacidity is a predisposing factor to protozoal infestation. Accordingly, decinormal hydrochloric acid was added to the flush solution in amounts varying from 30 to 210 c.c., increasing the free acidity of the whole wash to a maximum of 22 degrees to the Töpfer reagent. Six of these acid flushes were given in all, the last (tenth) flush of the series taking place on May 24, 1922.

The result of this acid flush treatment was disappointing. From the end of May to the end of June the patient suffered from persistent pain and had, in addition, an attack of diarrhea with as many as ten watery stools a day. In July, the symptoms subsided, but an eleventh bile drainage, carried out as a check at the end of September, still showed *Lamblia* present in the duodenum.

At this point it was decided to use neo-arsphenamin intravenously, according to the method of Carr and Chandler. Three injections, which were technically

difficult on account of the obesity of the patient and the smallness and inaccessibility of her veins, were successfully administered by Dr. Fred Wise, who reported his findings as follows:

"Miss L. M. received, on Oct. 7, 1922, a preliminary 'desensitizing' injection of 0.2 gm. neo-arsphenamin. There being no reaction within one hour, she received the balance of 0.7 gm. Except for a recurrence of her diarrhea during the following night, there were no untoward effects from the injection of 0.9 gm. neo-arsphenamin.

On October 12 the patient received 0.9 gm. neo-arsphenamin. Two days later there was a severe reaction manifested by conjunctival injection, headache, fever (102 F.), vomiting, pains in the chest and abdomen and diarrhea. The patient noticed that the stools had an unusual odor. The skin exhibited a universal erythematous eruption, in part also urticarial, associated with itching. After five days all symptoms subsided. There was no desquamation.

On October 28, the patient received the third and last injection of 0.9 gm. neo-arsphenamin. There was a moderate reaction two days later, in every way similar to that of Oct. 14, but very much milder. This subsided after three or four days and left the patient in an apparently normal condition.

The urine, examined between the days of the injections, was free from albumin and casts and sugar. At no time was there jaundice."

Duodenal drainage, performed on Oct. 22—ten days after the second injection of neo-arsphenamin—showed for the first time complete absence of *Lamblia* from the recovered fluid. On October 28, within an hour of the last injection, the duodenal tube was again introduced and the bile drained for from three to four hours. During this interval three stools were passed and collected. The bile (which was for the second time negative for *Lamblia*) and the stools were submitted to Dr. Joseph Felsen, who reported all specimens negative for arsenic by the Gutzeit method. The stools also failed to show either the free or the encysted forms of the parasite.

Subsequent Course.—In addition to the two negative bile drainages already mentioned (Oct. 22 and Oct. 28), ten more drainages were made during the six months since the treatment was given (see table). On every occasion the duodenal contents were free from every trace of *Lamblia* infection. In addition to the stool examination of Oct. 28, six subsequent tests (also shown in the table) likewise proved negative for this parasite.

As a contrast to the immediate cure of *Lamblia* infestation as such, the clinical condition of the patient has shown only partial amelioration. The liver can no longer be felt and the abdominal tenderness is much less marked and at times quite absent. There have been periods of diarrhea, however, lasting as long as ten days, with as many as ten stools during the twenty-four hours. At times there has been constipation. The bowels have moved loosely three or four times a day on the average, at least for the past few months. Occasionally there has been pain, both in the right side and in the back, worse on motion and interfering especially with walking and with stair climbing. In short, there is still some colitis and perhaps some cholecystitis, and it is probably too early to say just how much these factors have been affected by treatment.

NATURE OF THE CHOLECYSTITIS

That there was clinically an inflammation of the gallbladder is beyond question. It has already been pointed out that *Lamblia* does actually invade the gallbladder and that many, if not the majority, of the cases now being discovered by duodenal aspiration occur in patients suffering clinically from gallbladder trouble. Despite this fact, the most recent general works on diseases of the biliary passages fail to

mention this parasite as a possible factor in the production of biliary symptoms. Is it not time to add the concept of *Lamblia* cholecystitis to the other recognized forms of gallbladder infection?

Furthermore, in one of Simon's recent cases (Case 4) strikingly similar in its course to that in the case reported—the clinical observation was carried a step further in that the gallbladder was removed after arsphenamin injections had caused the disappearance of organisms from the bile, and that fresh scrapings from the gallbladder mucosa failed to reveal the presence of *Lamblia* organisms. It seems fair, therefore, to conclude that we have now strong evidence showing that a gallbladder infested with *Lamblia* can be actually freed from its protozoal invaders by the intravenous administration of arsphenamin. If this is really so, we are dealing with what is perhaps the first successful instance of a specific therapy for a known source of gallbladder infection.

Finally, it appears from the observation of our own case as well as that of others, that the elimination of the primary *Lamblia* infection is by no means synonymous with the cure, or at least with the immediate cure, of the associated cholecystitis. This may be because we still get the cases after the original parasitic insult to the biliary mucosa has developed into the ordinary chronic, nonspecific form of cholecystitis. It is to be hoped that the early recognition and treatment of giardiasis —that is, before the biliary symptoms occur—will lead to the complete elimination of this form of gallbladder complication.

NATURE OF THE REACTION FOLLOWING NEO-ARSPHENAMIN

Because of its delayed onset it may be assumed that the reaction experienced by the patient was not anaphylactic in the ordinary sense of the term. Perhaps the two most plausible explanations are the following: 1. The systemic upset may have been a response to the sudden destruction of enormous numbers of foreign organisms throughout the digestive tract with the liberation and absorption of hypothetic toxins. 2. The reaction may have been due to the neo-arsphenamin injection itself, owing to the failure on the part of a previously damaged liver to detoxicate the relatively large doses of arsenic which were required by the treatment. This would be in keeping with the accumulating evidence that many of the arsphenamin reactions are due to hepatic insufficiency.

Our failure to find arsenic in the intestinal contents (duodenal and fecal) after the injection of neo-arsphenamin is best explained—assuming that the tests were technically reliable—by the assumption that, owing to the presumably damaged state of the biliary and intestinal mucosa, the excretion of the heavy metal was delayed beyond the few hours during which our specimens were collected. It may also be

mentioned that the peculiar odor of the stools was not noticed by the patient until an interval of about two days after the injections.

COMMENT

What has been notably lacking in the cases published hitherto is the proof, by systematic reexaminations over sufficiently long periods after treatment, that patients are completely and permanently rid of the parasitic invaders. It has been my object, in the case reported, to make this demonstration as thorough as possible during the time interval available for this purpose. There is no question in my mind that the duodenum and the biliary system of my patient are free from *Lamblia*. It is perhaps possible that cysts from some focus lower down in the intestine have been overlooked in the stools. I hope to keep the patient under observation and to report results at some future time.*

CONCLUSIONS

1. *Lamblia* infection is sufficiently common to invite the diagnostic and therapeutic interest of all physicians.

2. The positive diagnosis of lambliasis may be made from an examination of the stools for cysts, or even more readily, of the duodenal contents for the flagellate forms.

3. *Lamblia* infection is manifested clinically by a colitis, with or without diarrhea, and probably commonly by an associated cholecystitis as well.

4. *Lamblia* infection cannot be uprooted by treatment with drugs acting only from within the intestinal lumen. We have in the intravenous administration of arsenicals (arsphenamin) a powerful and perhaps a specific method of attack. The success of this treatment is due to the secretion of arsenic by the entire gastro-intestinal and biliary mucosa, thus destroying not only the superficial but also the deep-seated (penetrating) protozoal parasites as well.

5. The initial dose of arsphenamin (or neo-arsphenamin) should be as large as possible (equivalent of 0.6 to 0.9 gm. neo-arsphenamin for an adult) so that *Lamblia* organisms do not develop an immunity as they might from smaller beginning doses.

6. In order to prevent or at least to detect a tendency to serious immediate reaction to the large dosage recommended, a preliminary small "desensitizing" dose (about 0.2 gm.) should be given. If no untoward effects occur within an hour, the rest of the initial dose may be safely administered.

* Since the foregoing was written, three more bile drainages (June, July and September, 1923) have similarly proved negative for *Lamblia*.

7. When, for any reason, intravenous arsphenamin therapy is not available, it is suggested that satisfactory results may be obtained by the intrarectal exhibition of this drug provided sufficiently large doses (4 gm. neo-arsphenamin) are made use of.

8. A case is reported of *Lamblia* infection associated with cholecystitis and colitis. The parasitic infection promptly responded to three injections of 0.9 gm. each of neo-arsphenamin and has remained cured, as shown by repeated reexaminations, for a period of half a year.

Synoptic Review of Therapy in a Case of Lambliasis

Serial Number of Bile Drainage	Date	Form of Therapy	Lamblia	
			In Duodenal Contents	In Stool
	(1922)			
1	May 3	Hypertonic saline flush	+	..
2	May 5	Hypertonic saline flush	+	..
3	May 8	Hypertonic saline flush	+	..
4	May 11	Hypertonic saline flush	+	..
5	May 12	Hypertonic plus n/10 hydrochloric acid 30 c.c.	+	..
6	May 13	Hypertonic plus n/10 hydrochloric acid 90 c.c.	+	..
7	May 15	Hypertonic plus n/10 hydrochloric acid 90 c.c.	+	..
8	May 19	Hypertonic plus n/10 hydrochloric acid 180 c.c.	+	..
9	May 21	Hypertonic plus n/10 hydrochloric acid 210 c.c.	+	..
10	May 23	Hypertonic plus n/10 hydrochloric acid 110 c.c.	+	..
11	Sept. 24	None	+	..
	Oct. 7	First dose of neo-arsphenamin 0.9g.	..	..
	Oct. 12	Second dose of arsphenamin 0.9	..	..
12	Oct. 22	None	0	..
13	Oct. 28	Third dose of neo-arsphenamin 0.9	0	0
14	Nov. 12	None	0	..
15	Dec. 3	None	0	..
	(1923)			
16	Jan. 14	None	0	..
17	Feb. 18	None	0	..
18	Mar. 10	None	0	0
19	Mar. 25	None	0	0
20	Apr. 1	None	0	0
21	Apr. 8	None	0	0
22	Apr. 14	None	0	0
23	Apr. 22	None	0	0

A STUDY OF THE BASAL AND NITROGENOUS METABOLISM IN A CASE OF ACUTE LEUKEMIA DURING ROENTGEN-RAY TREATMENT *

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The cases of acute leukemia in which the nitrogen balance has been studied have shown a marked nitrogen loss. Ebstein,[1] in 1889, reported a case which showed a twenty-four hour urea excretion of 62.7 gm. Magnus Levy,[2] in 1898, reported three cases. The first had a negative nitrogen balance of 24.8 gm. in forty hours, the second a negative balance of 85.4 gm. in seven days; the third, in which nitrogen intake was not calculated, a urinary nitrogen which averaged 21 gm. a day for seven days. Edsall,[3] in 1905, found in his case a negative nitrogen balance of 22.2 gm. in twenty-four hours.

We have not seen observations on the basal metabolism in acute leukemia, nor have we seen observations on the effect of radiation on the basal or nitrogenous metabolism of patients suffering from this disease. Patients with chronic leukemia almost invariably show an increased basal metabolic rate.[4] Following successful roentgen-ray or radium treatment the rate falls. Such a fall is usually coincident with reduction in the number of immature leukocytes.[5] Following radiation, there is increased excretion of nitrogen in the urine.[6]

REPORT OF A CASE

A girl, aged 18 years, entered the East Medical service of the Massachusetts General hospital on Jan. 21, 1921. Her family and past history were unimportant. She had felt well until three weeks before entrance. At that time, while

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* From the medical service and medical laboratory of the Massachusetts General Hospital, aided in part by a gift from Dr. William Norton Bullard.

1. Ebstein: Acute Leukämie und Pseudoleukämie, Deutsch. Arch. f. klin. Med. **44**:343, 1889.

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at her work in a shoe factory, she felt faint and feverish. She walked home and went to bed. Eight days before entrance she became jaundiced, with accompanying headache, nausea and vomiting. At this time, also, her mother noticed swelling of the cervical glands, and a few days later of the inguinal glands. Enlargement of the spleen had not been noted. Her weight was 20 pounds (9 kg.) less than it had been three months before.

On entrance to the hospital, the patient was pale. The cervical, axillary, epitrochlear and inguinal glands were greatly enlarged. The spleen reached to the umbilicus. Fundus examination of the right eye showed two patches of hemorrhage. The urine was negative, the red cells numbered 2,240,000, hemoglobin (Talquist) was 55 per cent., the bleeding time was thirteen minutes, and the clotting time (method of Lee and White[7]) the same. The leukocytes numbered 28,000; a differential count revealed 10 per cent. polymorphonuclears, 60 per cent. lymphocytes and 28 per cent large mononuclears. Of the red cells, 10 per cent. were reticulated and 17 per cent nucleated. On examination of the stained smear, Dr. George R. Minot found erythroblasts of all types present. There was almost no shape variation and slight variation in size, but all degrees of polychromatophilia were present. Young red cells were considerably increased. Eosinophils were rare, young polymorphonuclears numbered about 8 per cent. and the majority of the cells looked lymphoblastic.

There was some doubt concerning the acuteness of the disease, and it was decided to give the patient the benefit of this doubt and institute roentgen-ray treatment. After the first few weeks, however, the course of the disease was progressively downward. The red cells fell to one million, hemoglobin to 30 per cent. and the platelets to 70,000. The white cells were too immature to permit differentiation between the myelogenous and lymphatic forms of leukemia. Blood nonprotein nitrogen remained normal, but blood uric acid rose from 4.7 mg. per 100 c.c. of blood on the eighteenth day of the period of study to 8 mg. on the forty-first day. During the last two days of life there were extensive hemorrhages in the skin, intestines and urinary tract. Death occurred eleven weeks after the onset of symptoms. The short duration of the disease and the blood picture justified the diagnosis of acute leukemia. Unfortunately, permission for necropsy was not secured.

BASAL AND NITROGENOUS METABOLISM OF PATIENT

Soon after the admission of the patient, we decided to study her basal and nitrogenous metabolism. This was done for a period of fifty days, until death occurred. During this period the patient was on a weighed diet prepared by Miss Campbell, the hospital dietitian. The diet consisted of 65 gm. of protein (supplying 1.4 gm. of nitrogen per kilogram of body weight), 92 gm. of fat (on the thirteenth day increased to 116 gm., and 240 gm. of carbohydrate. This yielded about 2,050 calories, which was about 10 per cent. above the patient's basal requirement. Body weight throughout the period remained nearly constant.

The total nitrogen of the twenty-four hour urine was determined by the colorimetric method.[8] Stools were collected for a period of five days and the contained nitrogen was found to be 1.1 gm. per day.

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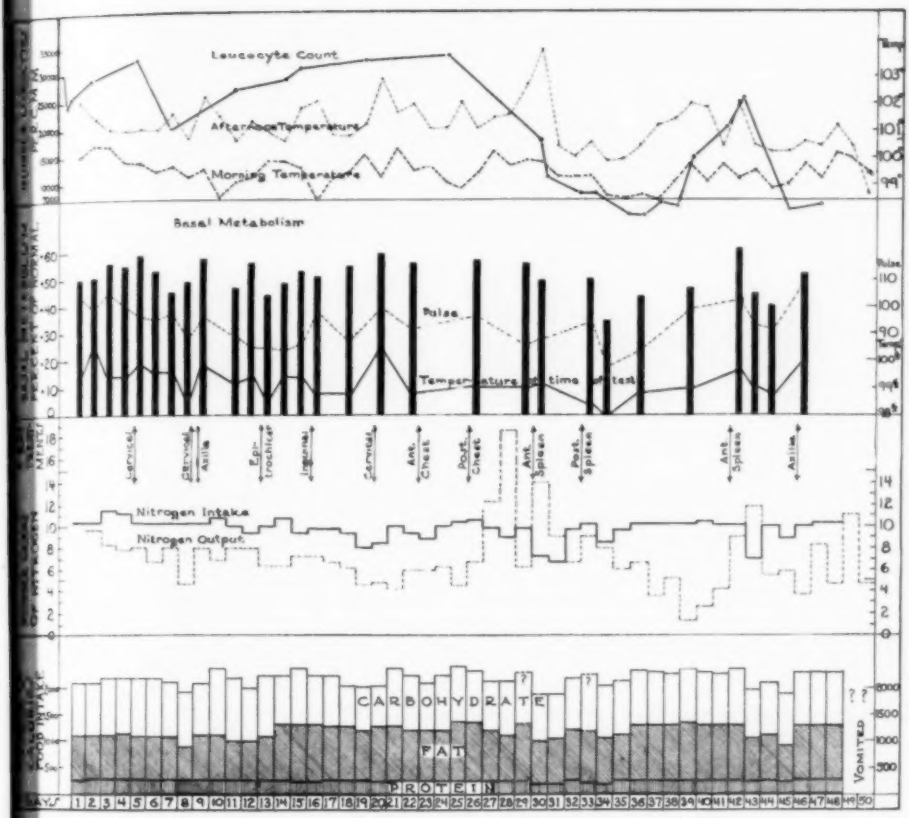

The days of observation are indicated at the bottom of the chart. Above this is the daily intake of fat, protein and carbohydrate, expressed in calories. Question marks indicate that an undetermined amount of food was lost because of vomiting. This amount was small, except on the last two days, when no food was retained. Above this a solid line marks the grams of nitrogen contained in the food and a dotted line the grams of nitrogen excreted in urine and feces. The double headed arrows indicate the days on which roentgen-ray treatments were given. The words "cervical, axillary," etc., denote the glands which were irradiated. Basal metabolism is represented by solid columns which express the percentage increase above the metabolism of a normal person of the same age and sex and of equal surface area. The solid line connecting these columns indicates the temperature, and the broken line the pulse, at the time of the test, about 11 a. m. At the top of the chart, the lower broken line indicates the early morning temperature and the upper broken line the evening temperature. The solid line represents the leukocyte count.

This average amount was added to the urinary nitrogen to give the nitrogen output. Unmeasured but small amounts were lost through occasional nose bleed. During the last two days nitrogen loss through hemorrhage was large. The patient did not menstruate during the period of study. Oxygen consumption was measured by means of a Benedict portable apparatus. Determinations were made with the patient in her own bed in the ward. In order to interfere as little as possible with the patient's meals, determinations were made four hours after her breakfast, a meal largely carbohydrate containing about 500 calories. Oxygen consumption was thus measured under standard, rather than under basal, conditions. Separate experiments on normal subjects showed that in four hours after a meal of this type the metabolism had returned to within 5 per cent. of its basal level. Roentgen-ray treatments were given under the direction of Dr. George W. Holmes. In each exposure a suberythema dose was used.

SUMMARY

The principal data of this study are presented graphically in the chart. Inspection of the chart reveals these facts:

1. The patient maintained a positive nitrogen balance of a gram or two on a normal nitrogen intake of about 10 gm. a day. This finding is contrary to the observations quoted in the beginning paragraph. Our patient showed an unusually low leukocyte count. Apparently the processes of cellular metabolism, such as the relative intensity of leukocyte production and destruction, were different in our patient and those previously reported. This question of the level of nitrogenous metabolism in acute leukemia deserves more extended study.

2. The nitrogen balance was little affected by roentgen-ray exposure of the superficial lymph nodes. Radiation of the thoracic glands and the spleen, on the other hand, produced a marked increase in urinary nitrogen. This effect was, however, transitory.

3. Leukocyte count and nitrogen balance were, in a general way, reciprocal factors. A rising leukocyte count accompanied nitrogen retention, and a falling count nitrogen loss.

4. Leukocyte count, temperature and basal metabolism moved together. The leukocyte count was, however, more labile than the other two. On two occasions the count fell to normal. At these times the evening temperature remained elevated and the metabolism was but little affected. The metabolism seemed to be a truer indicator of the severity of the process than the leukocyte count.

MELANURIA WITHOUT MELANOSARCOMA *

REPORT OF A CASE

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NEW HAVEN, CONN.

This case is reported because of the occurrence of melanuria without any evidences during life or at postmortem examination of any abnormal source of production of the pigment.

CASE REPORT

History.—W. S., a school boy, aged 13, born of American parents, was admitted to the New Haven Hospital on March 6, 1922, complaining of progressive enlargement of his abdomen and increasing weakness and drowsiness. His family history was not significant. His past history was unimportant except for frequent nose bleed since childhood and headaches occurring with increasing frequency for a year before admission to the hospital. Three months before admission the patient noticed that his abdomen was growing larger. At the same time he began to complain of a constant tired feeling. His mother noticed that he seemed drowsy all the time, and his teacher complained that he fell asleep at school. He also became irritable. Although his weight increased constantly, his appetite diminished. As the enlargement of his abdomen continued, he developed increasing shortness of breath on exertion. His skin also became sallow and yellowish. A week before admission he began to vomit. The vomiting occurred every other day, usually after a meal, the vomitus consisting of thick, yellowish material. With the onset of the vomiting he began to have a slight, dry cough.

Physical Examination.—Examination on admission revealed a well developed, moderately well nourished boy, lying quietly in bed, apparently in no distress, mentally clear, but rather drowsy and apathetic. His respirations were somewhat rapid and shallow. His skin and mucous membranes were pale, with a slight yellowish tinge, but there was no definite icterus. His hair was black, his natural color apparently somewhat dark, with small freckles on his nose, but no evidences of any abnormal pigmented lesion. There were small, herpetic lesions on both lips. His tonsils were moderately enlarged but showed no signs of active inflammation. His lungs showed dulness behind extending as high as the scapular angle on the left and somewhat higher on the right side. Over these areas breath and voice sounds were diminished. The cardiac impulse was diffuse and forcible, extending 14.5 cm. to the left, well beyond the nipple line. Auscultation revealed a systolic murmur, maximum over the pulmonic area, but transmitted also to the apex. The pulse was regular—rate 82—and of good quality. The blood pressure was: systolic, 110; diastolic, 60. His abdomen was protuberant, rounded, smooth and tense, with distinct dulness in the flanks and a fluid wave. In the left hypochondrium was a large mass, extending about 7 cm. below the costal margin in the direction of the umbilicus, presenting a sharp edge and descending slightly on deep inspiration. In the midline a sharp edge could be felt about 4 cm. below the xiphoid, but no liver edge could be felt in the right hypochondrium. There was moderate, pitting edema of the feet, legs, thighs and lower part of the trunk. There was no general lymphatic enlargement. The reflexes were normal.

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* From the department of internal medicine of Yale University and the medical service of the New Haven Hospital.

Laboratory Examinations on Admission.—Radiographic examination of the chest and abdomen revealed right hydrothorax; the left side of the chest was clear, but the heart was displaced to the left; the splenic tumor gave a distinct shadow, but the liver did not appear to be enlarged. The blood count revealed: red blood cells, 3,300,000; hemoglobin, 70 per cent; white blood cells, 6,100; polymorphonuclears, 65 per cent.; lymphocytes, 28 per cent.; large mononuclears,

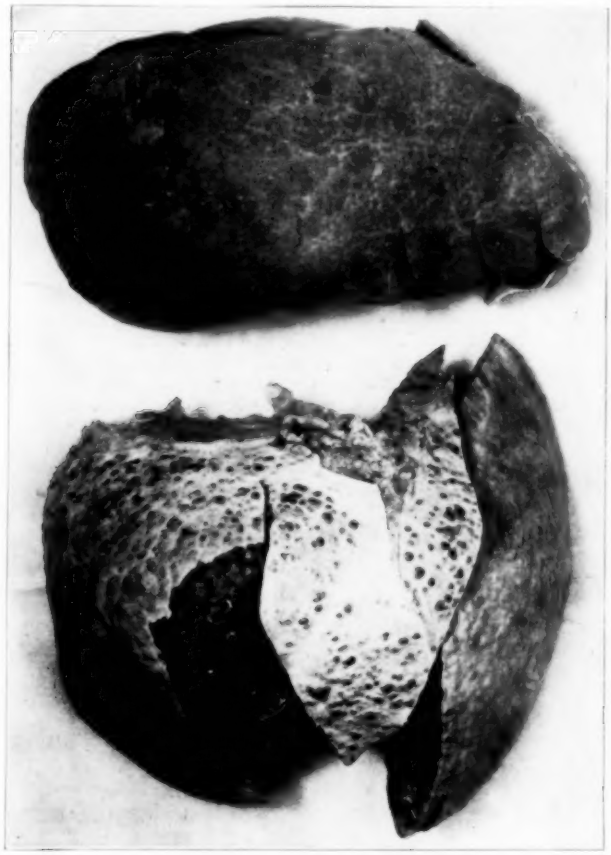

Fig. 1.—Spleen above and liver below, showing the gross pathologic changes and the comparative size of the two organs.

6 per cent.; eosinophils, 1 per cent. Smear showed moderate achromia; there were no nucleated red cells nor basophilic stippling. The urine was light yellow and acid. The specific gravity was 1.019; there was no albumin or sugar. The sediment was negative. The Wassermann test was negative. Intracutaneous tuberculin ($\frac{1}{50}$ mg.) gave a positive reaction. The chest fluid and abdominal fluid were both sterile and of rather low specific gravity, with cells, pre-

dominantly lymphocytes. No tubercle bacilli could be found on direct smear, and guinea-pigs that had received injections failed to developed signs of tuberculosis.

Course.—Throughout his stay in the hospital the physical signs remained about the same. There was a constant accumulation of fluid in the abdomen and chest that demanded repeated paracentesis. After the first few days in the hospital he began to show an irregular temperature, rising at times as high as 102 F. Blood cultures were negative, and there was no leukocytosis. Shortly after admission he developed a mild diarrhea, which lasted three or four days. At about the same time the subcutaneous edema increased rapidly, urine volume diminished, and the salt output was found to be very low. The urine showed no morphologic changes, however.

On March 27, three weeks after admission, he was suddenly seized with severe pain in the left flank, not radiating, accompanied by vomiting of undigested food. The vomiting did not relieve the pain. Some diffuse tenderness was found in the left flank, and red blood cells appeared in the urine. The tenderness and hematuria lasted only a few days. About this time, distention of the abdominal veins became quite striking.

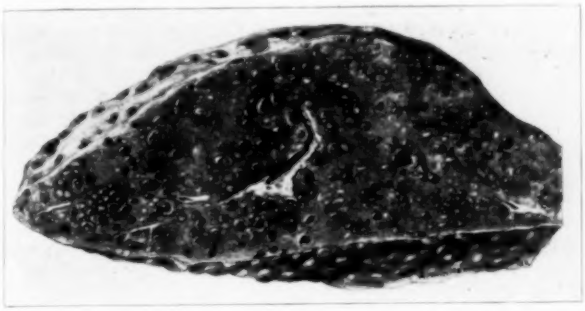

Fig. 2.—Cross section of liver showing the small islands of liver tissue and the greatly increased connective tissue between them.

The retention of salt and water increased in spite of the most rigid dietary restrictions. At times as little as 0.1 gm. of sodium chlorid was found in a twenty-four hour urine specimen, and the total urinary output was usually less than 500 c.c. From time to time, usually in the morning, he vomited material containing food particles. Anemia increased slowly, but the yellow color of his skin became more marked.

Although it was evident that his general condition was deteriorating in spite of the temporary relief of symptoms afforded by repeated paracentesis, no marked change occurred until the morning of May 12, when he had a sudden attack of vomiting before breakfast. From this time on vomiting was persistent, and he suffered from distressing upper abdominal distention that resisted all efforts to relieve it. He became steadily weaker, and died in the morning of May 14.

Additional Laboratory Findings.—Blood nonprotein nitrogen on March 8 was 25 mg. per 100 c.c.; on March 29, 28 mg.; postmortem, 91 mg. (blood urea nitrogen, 21 mg.). Blood sugar on March 8 was 116 mg. per 100 c.c. The urine gave no reactions for bile until three or four days before death. Plasma obtained at necropsy was distinctly bile stained, but the abdominal fluid contained no bile.

Necropsy.—Because of restricted permission, necropsy was performed through a small abdominal incision. The organs, with the exception of the liver and spleen, were examined in situ and not removed.

The conjunctivae and the skin of the body were pale and had an icteric tint, but showed no pigmented lesions. The face, trunk and extremities appeared edematous. The abdomen was greatly distended, and the superficial abdominal veins were prominent. The peritoneal cavity contained approximately 2,000 c.c. of clear, thin amber fluid. The vessels of the parietal peritoneum were enlarged and prominent. The abdominal contents appeared to be normally disposed. The lower pole of the spleen projected below the costal margin on the left side. The liver edge lay beneath the arch of the ribs. The stomach was moderately full, and the wall of the upper portion of the small intestine was dark. The right pleural cavity contained 500 c.c. of straw colored fluid. The left pleural cavity contained no excess of fluid. There were no adhesions on either side. In the pericardial sac there were about 25 c.c. of clear, pale fluid.

The heart was not removed, but appeared, as viewed through the abdominal incision, to be small and normal. The right lung, examined in the same way, appeared collapsed and atalectatic; the left lung was large, voluminous and crepitant.

The stomach contained a large amount of blackish red, grumous material. The vessels of the mucosa were injected. The duodenum contained bile and a quantity of material similar to that found in the stomach. The upper 6 feet (182.8 cm.) of the small intestine contained material like that found in the stomach. The submucosal vessels were intensely injected in many places. Otherwise, neither small nor large intestines showed any abnormalities. The bile and pancreatic ducts joined and emptied at the ampulla of Vater, and were all patent. The pancreas was not removed, but section in situ revealed no gross changes in the organ.

The suprarenals showed no striking abnormalties.

The kidneys were not removed. They were of average size. On section, in situ, the capsules stripped readily; the markings were distinct, the cortex normal in thickness. The entire organs had a distinct yellowish green tint.

The spleen weighed 325 gm. and measured 17 by 8 by 3 cm. It was firm and retained its shape after removal. The capsule was smooth. There were three small notches anterior to the proper hilus. On section it was firm, maroon in color, and the trabeculae were prominent. The cut surface was smooth, but did not protrude. The pulp was not excessive, and the malpighian bodies were not discernible.

The liver weighed 525 gm. and measured 15 by 12 by 7 cm. Its surface was roughened by projecting, yellowish brown nodules which averaged from 3 to 4 mm. in diameter. The capsule was thickened and wrinkled. The organ cut with resistance and the cut surface was everywhere marked by small yellowish green nodules from 3 to 4mm. in diameter, projecting from the surface and separated by grayish brown zones. Some of these nodules were definitely bile colored. The central veins were not prominent, and the destruction of liver lobules was not apparent. The striking changes were the hobnail appearance, the decrease in size of the organ, and the increase of connective tissue in all portions.

The gallbladder contained a small quantity of yellowish green bile, together with considerable tenacious mucus.

Microscopic Notes.—The lungs, pleura, stomach, intestines, pancreas and suprarenals showed no remarkable abnormalities.

In the kidneys, the epithelium of the convoluted tubules was swollen and granular, and the nuclei showed various stages of degeneration, but the lumina of the tubules were free. The blood vessels of the glomeruli and the pyramids were well filled, and the tubules in the pyramids were unchanged.

In the spleen, the malpighian corpuscles were reduced in number, and some had about their periphery an accumulation of red blood cells forming a dense boundary. The sinuses were well filled with red and white blood cells, and the fibrous reticulum was markedly increased.

The architecture of the liver was altered so that there were everywhere circular zones of cells surrounded by dense bands of connective tissue. The liver cells were granular and pale staining. They showed changes of degeneration, and in some areas were lacking in nuclei and had protoplasm that stained a homogeneous, pale pink. These cells were necrotic. In many zones the

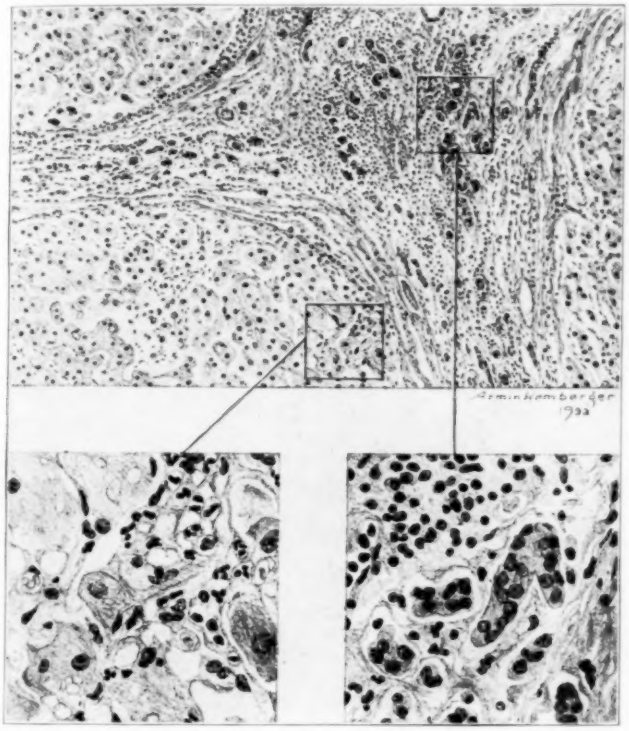

Fig. 3.—Microscopic sections of liver tissue, illustrating the loss of normal hepatic structure and the increase of fibrous tissue. The high power sections show the character of the degenerative changes in the liver cells, regeneration from the bile duct cells and the nature of the infiltration with both polymorphonuclear and mononuclear cells. There is no evidence of excessive pigmentation.

spaces between the liver cells were filled with polymorphonuclear leukocytes, and in several of the circular masses there were spaces left vacant by the disappearance of liver cells. These areas were filled with connective tissue. The fibrous tissue surrounding the liver cells was dense, and in it were many mononuclear cells and numerous bile ducts, some of which were in continuity with liver cells and appeared to be proliferating. In some zones polymorpho-

nuclear leukocytes were found in great numbers in the tissue. There was fat everywhere in the form of small and large droplets. The central veins were not easily identified, and the hepatic artery, portal vein and bile duct usually found at the periphery were much distorted.

Stains for fat and iron on liver sections showed a great quantity of fat in the organs, but essentially no iron.

The anatomical diagnosis was cirrhosis of the liver, chronic splenic tumor, ascites, hydrothorax, jaundice and hemorrhage into the stomach and duodenum.

For some time before his death the urine contained constantly large amounts of a chromogenic material that gave all the typical reactions of melanin. This was first discovered accidentally. The urine of another patient, A. G., suspected of advanced melanosarcoma, was tested for melanin. It gave typical

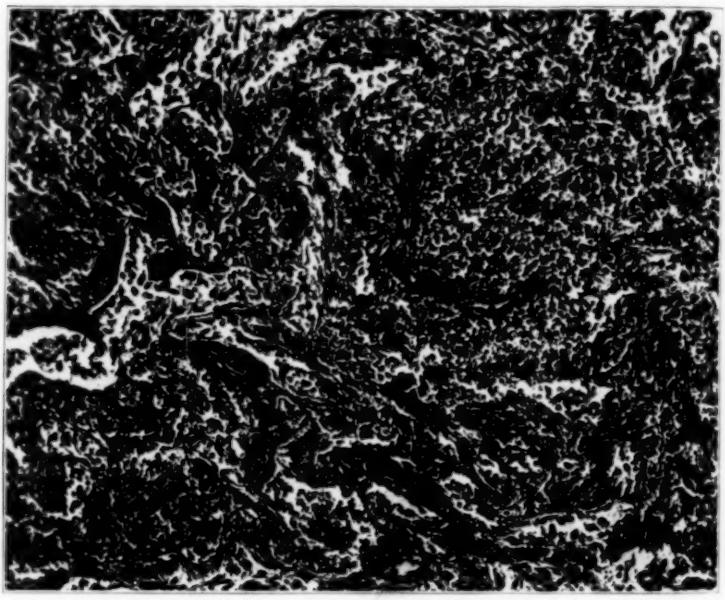

Fig. 4.—Microscopic section from spleen.

reactions after the addition of oxidizing agents, although it darkened only slightly when exposed to the air at room or icebox temperature. As a control, a specimen of urine from W. S. was exposed to the same oxidizing agents. The only reasons for choosing this specimen were that it was the most highly colored, concentrated urine at hand. After oxidation with bromin water and with ferric chlorid a definite black precipitate formed, which was almost as marked as that formed in the urine of the patient suspected of melanosarcoma. It seemed so inconceivable that W. S. could be excreting melanin that the only immediate result of this observation was to cast doubt on the specificity of the tests.

An exploratory operation, however, confirmed the diagnosis of melanosarcoma with extensive metastases in A. G. Shortly after this it was noticed that on some days W. S.'s urine became distinctly dark on standing. Repeti-

tion of the oxidation tests revealed even larger amounts of melanin than were found on the first occasion and further investigation was undertaken a few days before the patient's death.

Although the urine on some days was distinctly dark, there was little tendency to spontaneous oxidation at room temperature. The urine was highly colored with urobilin and some bile and showed a heavy precipitate of urates on standing. After only a few minutes on the steam bath, it became very dark, and a black precipitate slowly settled out. The addition of bromin water, ferric chlorid or nitric acid produced a similar precipitate. The precipitate formed after the addition of bromin water or nitric acid dissolved in carbonate solution, but could be reprecipitated by acidification with hydrochloric acid. It was difficult to obtain solution of the ferric chlorid precipitate because of the heavy precipitate of phosphates that was produced in the reaction. Solution and reprecipitation could be repeated indefinitely by the alternate addition of alkali and acid. The urine did not become dark after the addition of alkali, nor did it reduce alkaline copper solutions.

Several other urines have been subjected to the same treatment with entirely negative results. Among those chosen were specimens from: (1) a patient with moderately advanced hypertrophic cirrhosis of the liver and ascites; (2) a patient with symptomatic purpura, venous thrombosis, compensated cardiac valvular disease and enlarged liver (this urine contained considerable urobilin); (3) a patient with carcinoma of the head of the pancreas and complete biliary obstruction, with a large liver; (4) a patient with carcinoma of the stomach, severe anemia and extensive metastases in the liver; (5) a patient with Banti's disease.

ISOLATION OF MELANIN

When it became clear that the material was undoubtedly melanin, an attempt was made to isolate it. As this was begun only three days before the patient's death, the amount recovered was not great. The method of isolation described by von Jacksch (precipitation by basic lead acetate, removal of the lead by filtration after treatment by hydrogen sulphid and evaporation of the filtrate) proved unsatisfactory.

In the urine of A. G., the patient with known melanotic sarcoma, the lead acetate removed the pigment, but it proved impossible to liberate it without great loss from the lead sulphid precipitate. The method finally employed consisted of: (1) development of the color and concentration of the urine by partial evaporation on the steam bath; (2) precipitation by bromin water after acidification with concentrated hydrochloric acid; (3) recovery of the precipitate by centrifugalization; (4) repeated solution and reprecipitation in large centrifuge tubes by the alternate addition of strong sodium carbonate solution and concentrated hydrochloric acid (the latter added drop by drop until somewhat beyond the point of cessation of effervescence); (5) washing of the precipitate with 0.1 normal hydrochloric acid.

The first precipitation was always incomplete, the supernatant fluid remaining highly colored. Further concentration of the fluid yielded another precipitate. Even repeated concentration, however, failed to

remove all the color from the original fluid. Some color was apparently lost in the first reprecipitation also. After the second reprecipitation, however, the supernatant fluid came away practically clear. With the first precipitate a large admixture of acid salts was obtained. These were washed out and carried away in subsequent precipitation. It was later found that repeated washing of the first precipitate with 0.1 normal hydrochloric acid hastened this process. The first precipitation, however, was more complete in highly acid solutjons.

Because of the relatively small amount of urine available, no attempt was made to obtain the unoxidized melanogen by the method of Eppinger. It seemed safer to try for the melanin alone, because the latter by its color afforded constant evidence of its presence and an indication of the efficiency of the methods employed for its recovery.

An analysis of the material was made by Miss R. B. Hubbell in the department of physiological chemistry. The complete report of her studies will be published elsewhere. These studies, however, confirmed our findings. The pigment gave all the usual reactions for melanin. For comparison, a sample of melanin made from black hair and a small amount obtained from the urine of A. G. were also analyzed. The results for nitrogen, ash, and sulphur are shown in the table.

Results of Analyzing Melanin from Black Hair and from Urine

Sample	Nitrogen (Ash-Free)	Ash	Sulphur	Iron
From hair	12.80	1.60	2.50	0
W. S.	11.00	11.90	2.21	0
A. G.	8.72	3.34	—	0

The amounts of nitrogen and sulphur were quite comparable to those obtained from the sample of prepared melanin and agree with analyses of melanin found by others in urine from patients with melanotic sarcoma. The nitrogen in the sample from A. G. was considerably lower. The sulphur content was also quite typical. On the other hand, the ash from the W. S. sample was very high. This may well be due to impurity. The amount of material available was not sufficient to permit attempts at further purification.

A study of the solubilities of the pigment gave some rather interesting results. Besides the ordinary solubilities which are described as the characteristic properties of melanin, the material from W. S. also showed some distinctive atypical solubilities. It dissolved freely in amyl alcohol and to a lesser extent in butyl alcohol and ethyl alcohol. The specimen obtained from hair proved insoluble in all these solvents, and the sample from A. G. was only slightly soluble in butyl alcohol and insoluble in amyl and ethyl alcohol. The color of these solutions

was quite similar to that of the alkaline solutions. Spectroscopic examination of the solutions revealed no absorption bands in the visible spectrum.

COMMENT

So far as we have been able to determine, this is the first case in which melanuria has been reported as occurring in a person who showed no evidence of the presence of a pigmented tumor. What is perhaps more remarkable is the fact that none of the important viscera showed any abnormal pigmentation of the melanotic type. The patient was of the black haired, dark skinned type, indicating a natural tendency to pigmentation, but the skin revealed no localized areas of excessive pigment deposition. There was nothing in the chemical analyses of the urinary pigment that differentiated it from other specimens of melanin.

The striking pathologic lesion discovered at necropsy was an extreme reduction of liver substance, apparently due to a destructive inflammatory condition which the patient had survived long enough to permit considerable repair and connective tissue replacement. Unless we except the melanuria, there is nothing in the clinical or pathologic picture that cannot be adequately accounted for on the basis of such a lesion alone. The question may reasonably be raised whether the melanuria was not also dependent on the hepatic lesion.

Eppinger,[1] in an extensive review of the subject, claims that the mere presence of a melanotic sarcoma in the body, no matter how extensive, will not produce melanuria. Melanin, he says, appears in the urine only after the liver has been extensively invaded by metastases. He argues from this that the normal liver breaks down melanin that escapes into the circulation. Only when the liver is injured sufficiently to impair its ability to destroy melanin does the latter appear in the urine. It is conceivable that some of the melanotic pigments that produce the normal coloration of a dark person might find access to the blood and, in the absence of normal liver function, fail to be destroyed and thus pass into the urine. This could, however, hardly account for the melanuria in this case, because the quantities of pigment recovered were too great. The amount obtained in three days was more than 1 gm., the total estimated amount of coloring matter found in the skin and hair of a dark negro. In spite of the negative clinical and pathologic findings, an excessive production of melanin must be assumed, the source of which remained undiscovered.

The case is of interest because it indicates that melanuria can occur in the absence of melanotic sarcoma. If investigation of similar cases reveals the same condition, a new light may be thrown on the metabolism of this interesting group of pigments.

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THE VALUE OF THE ELECTROCARDIOGRAPH IN PROGNOSIS

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The electrocardiograph has definitely established itself as an invaluable aid in the diagnosis of the arrhythmias. In this respect, it is universally admitted that it is superior to the polygraph. As a rule, electrocardiographic tracings give us a clear-cut picture of the mechanism of the heart, the spread of the excitation wave and the presence or absence of an abnormal rhythm.

The additional data made available through electrocardiographic studies can be applied clinically with great advantage to both the patient and the physician. With this additional knowledge that the electrocardiograph has placed in the hands of the physician, he is able in most instances to make the correct diagnosis of an arrhythmia by physical examination alone. Nevertheless, when any question arises regarding the precise mechanism of the heart, the electrocardiograph becomes the court of last resort.

Within the last few years, as the result of innumerable tracings and the researches of many investigators, the electrocardiograph has come to be regarded as having some additional value to the clinician in the way of prognosis. As prognosis constitutes one of the most important aspects of a cardiac case, any measure which may throw additional light on this vital matter should be utilized as a routine procedure.

We are able with a fair degree of certainty to diagnose by clinical means the state of the various valves of the heart. The condition of the conduction system of the heart at any given time can be determined by the electrocardiographic tracing. But even knowing the state of the valves and of the conduction system, we are still left more or less in the dark as regards the condition of the cardiac muscle itself, which, after all, is probably most important in the vast majority of cardiac cases.

We have attempted to devise functional tests which will give us information regarding the state of the cardiac muscle. The great number of these tests proposed is in itself evidence that no test is enirely satisfactory. Each of the various tests devised depends for its result not only on the integrity of the heart muscle but also on the nervous mechanism, the respiratory apparatus, the state of the blood

and, in fact, on such a great variety of bodily activities that the condition of the heart itself may be entirely obscured and gravely erroneous conclusions reached.

Since the advent of the electrocardiograph, attempts have been made to correlate the findings of abnormal deflections in electrocardiographic tracings with definite pathologic conditions of the heart muscle. While data on this particular point are still in the process of being formulated, we may safely say that certain of these abnormal deflections are coming to be regarded more and more as indicative of myocardial damage.

The two groups of deflections which have been particularly regarded with significance are the Q-R-S group and the T-waves.

The Q-R-S group normally should not exceed one-tenth of a second in duration, and in a tracing that shows a longer duration we are justified in assuming that there is defective conduction through one or the other ventricle. Again, a notching of the Q-R-S group in leads other than Lead III has come to be regarded as additional evidence of myocardial damage. Occasionally we find this abnormal width of the Q-R-S group associated with a notching or slurring of the waves. The conduction system is regarded as specialized heart muscle, and constitutes only a small percentage of the total heart muscle tissue. We know that it may be disturbed functionally without necessarily being organically damaged. In cases in which the conduction system shows this evidence of persistent impairment, it does not necessarily follow that the rest of the cardiac muscle is also impaired.

Nevertheless, in many cases, organic disease of the heart is an accompaniment of a defective conduction system. The heart may recover from widespread infection, leaving some residual scar tissue. If this should happen to be in some part of the conduction system, we may get rather startling electrocardiograms in an otherwise normal person. It would seem rather infrequent, however, for this relatively small area of the heart to be damaged without affecting other areas in the myocardium.

The other group of deflections which have come to be regarded as giving us some information concerning the state of the myocardium are the T-waves. Normally these waves are upright, although occasionally in Lead III we may find them inverted, and an inversion of the T-wave in Lead III is usually regarded as of no particular significance. However, an inversion of the T-wave in Lead I or II, or both, or in all three leads, cannot be disregarded. The association of these abnormal deflections, in leads other than Lead III, with definite myocardial damage, has now been demonstrated sufficiently often to render their occurrence in a given case a rather bad omen.

It must be kept in mind, however, that the heart is able in many instances to recover from the effects of toxins or bacterial invasion and that one must exercise great care in invariably giving a bad prognosis, even when definite signs of myocardial injury can be demonstrated.

It is well known that the best cardiac drug in our possession, namely, digitalis, may produce significant changes in the electrocardiographic tracing, such as an inverted T-wave and a definite prolongation of the conduction time. Yet no one would go as far as to say that digitalis produces a myocarditis, and we see that when the drug is discontinued these changes in the tracing eventually disappear.

The same thing may be said of the acute infectious diseases. The heart may become involved during the course of these diseases and a definite myocarditis produced with significant changes in the electrocardiogram, and it is well for the cardiologist to exercise some self-restraint in giving his prognosis, even though it may be backed up by significant abnormalities in the electrocardiogram. It is not unusual for these abnormalities to disappear entirely as the patient recovers and the heart gradually regains its normal capacity. Nevertheless, these abnormalities occurring in any given case should serve to focus attention on the heart, and the patient in every instance should have careful supervision, adequate rest and a routine tending to safeguard the heart until it has regained its normal functional capacity.

It is in cases in which these abnormalities in the electrocardiogram persist that we feel more at liberty in using the tracing for prognostic purposes. Their prognostic import becomes all the more significant in those cases in which the history of acute illness is absent or remote, and in which the symptoms of heart failure come on suddenly as in an anginal attack, or insidiously as in the common type of chronic myocarditis.

The lesions most frequently found associated with this abnormality of the electrocardiogram are probably hypertension, chronic myocarditis, arteriosclerosis, angina pectoris, hyperthyroidism, chronic nephritis and disease of the coronary artery. The outstanding cardiac lesion in the majority of these cases is usually a fibrosis replacing and encroaching to some extent on the cardiac muscle.

A normal electrocardiogram, on the other hand, can never be regarded as indicating a perfectly healthy myocardium.

Pardee and Master state that ventricular muscle disease is a far more important deduction from the finding of abnormal ventricular waves than it has been heretofore considered, so that the clinical importance of abnormal electrocardiograms becomes more apparent.

Willius states that significant T-wave negativity and an abnormal Q-R-S complex in all deriviations is of the greatest value from the

standpoint of prognosis and justifies the use of the electrocardiograph as a valuable clinical adjunct.

Wilson states that when the T-wave is completely inverted in Lead I or II and the patient has had no digitalis, cardiac diseases may be diagnosed with a fair degree of certainty even when the Q-R-S group is normal.

As illustrating the type of patient to which we refer, a case is reported, with electrocardiographic tracings and postmortem findings.

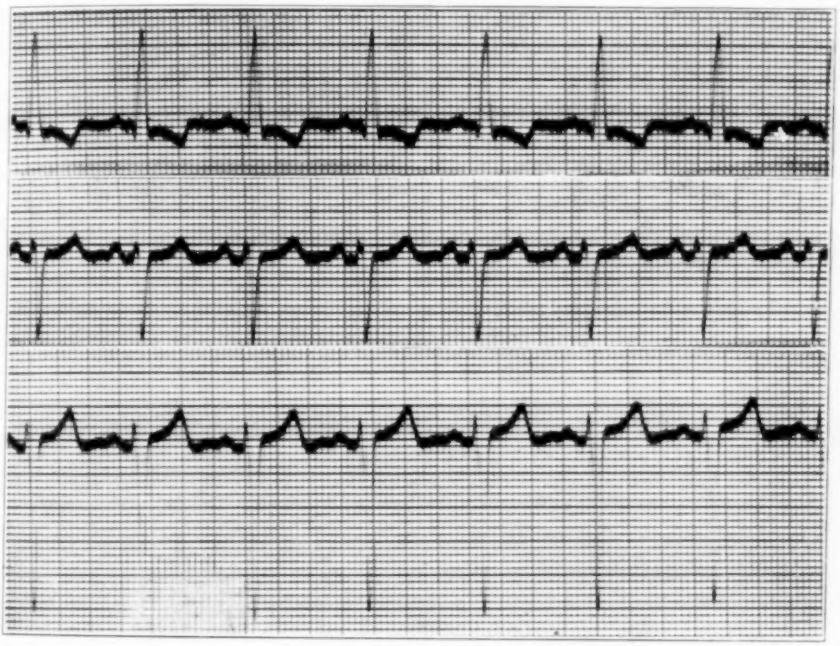

Fig. 1.—T-wave in Lead I is inverted, and there is some increase in the Q-R-S interval. Time in fifths and twenty-fiifths of a second.

REPORT OF A CASE

History.—A man, aged 71, had been in excellent health until within a few months before examination. He complained of some shortness of breath on exercise, although not sufficient to incapacitate him to carry on his duties, which were largely of a supervisory character and involved little physical exertion.

Examination.—Physical examination revealed a rather marked tortuosity of the superficial arteries and the retinal arteries, which showed evidence of sclerosis. The blood pressure was: systolic, 212; diastolic, 112. There was a blowing systolic murmur over the apex, and the aortic second sound was rather loud and ringing in character. Occasionally there was a reduplication of the second sound at the base.

The Wassermann reaction was negative; the urine showed albumin and granular casts and the blood showed a nonprotein nitrogen of 45 mg.

The electrocardiograph at this time showed a rapid rate which was quite regular. There was marked left side preponderance. The P-R interval was normal. The P-waves were upright and normal in appearance in the three leads. The Q-R-S interval exceeded one tenth of a second and could therefore be said to be definitely prolonged. The T-wave was inverted in Lead I. Figure 1 contains the electrocardiograms taken at this time. Eighteen days later the electrocardiogram showed no essential change from previous tracings except for a brief period of extrasystoles arising in the right ventricle and occurring at every other beat. Figure 2 contains these tracings. Two weeks after the

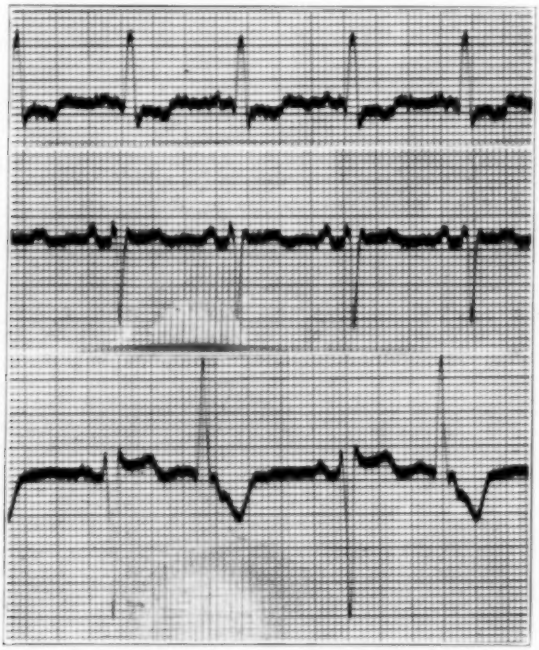

Fig. 2.—A brief period of extra systoles arising in the right ventricle. The inversion of the T-wave in Lead I and the increased Q-R-S interval persist.

second electrocardiogram was taken a third electrocardiogram showed that the resistance was 1,800 ohms; the rate 62 and regular; the P-wave upright and normal in the three leads; the P-R interval 0.18 seconds; there was left side preponderance and notching of the S-wave in Lead II; the Q-R-S interval was 0.12 seconds; the T-waves were inverted in Leads I and II, upright in Lead III; following exercise the rate became 95 and one premature contraction arising in the auricle was seen, and after two minutes' rest the rate was 72. Figure 3 shows the tracings taken at this time.

Course of Illness.—In view of these findings, together with the result of the physical examination, a grave prognosis was made. The patient, however, refused to remain in bed and went about his duties as usual. Ten days after the third electrocardiogram was taken, the patient died suddenly.

Necropsy.—The postmortem examination of the heart by Lieut. R. M. Choisser, M. C., U. S. Navy pathologist at the Naval Medical School, revealed that the heart was large (600 gm.) for the size of the person. The epicardial fat was yellowish and normal in amount. The superficial vessels were prominent and distinctly tortuous. The coronary arteries were sclerosed and noncompressible. Their outline was irregular because of the deposition of calcareous material. The anterior coronary artery when opened showed the lumen narrowed throughout by sclerosis and calcium deposits. In the descending branch, at a distance of 11 cm. from its origin, the lumen became distinctly narrow and was completely occluded by a large calcareous plaque. No gross lesions were demonstrable in the myocardium below this point. The lumen of the posterior coronary artery was also similarly narrowed throughout its course. It showed in its descending branch, 5 cm. from its origin, a definite narrowing,

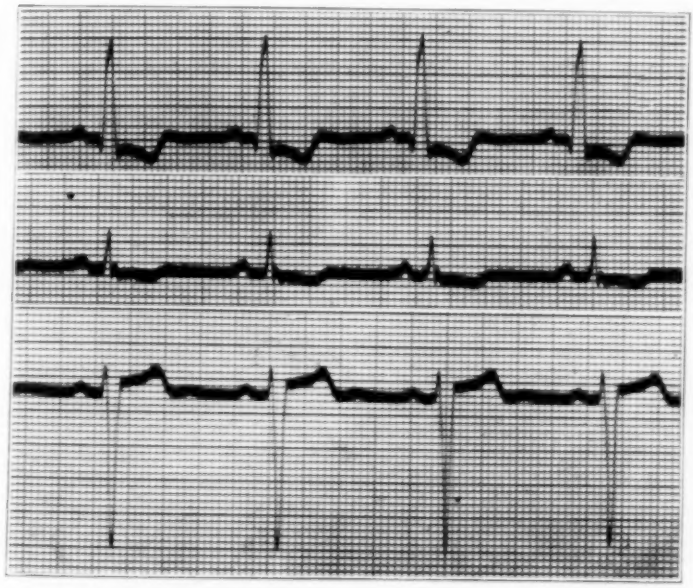

Fig. 3.—Inversion of the T-wave in Leads I and II. The Q-R-S interval is 0.12 seconds. The tracing was taken ten days before the death of the patient.

which amounted to almost an occlusion. The tricuspid valve measured 12 cm. The right ventricular wall was brownish and 11 cm. in thickness. The pulmonary artery showed a few areas of atheromatous changes, normal cusps and valve measurement of 6 cm. The left auricle was normal, with a wall measurement of 7 cm. The myocardium of the left ventricle was light brown with whitish areas of fibrous tissue throughout; it was markedly hypertrophied, being 2 cm. in thickness. The aorta showed atheromatous changes and plaques of calcium deposit. The valve measured 7 cm.

On microscopic examination of the coronary arteries, the media showed little change in structure, although its outline was irregular because of the protruding structures below. The intima was markedly thickened and irregular. Fibrosis was marked, and some areas showed an accumulation of small round cells. A calcareous deposit was seen throughout. In the places in which

extreme narrowing occurred, it apeared to be all that remained of the original coat. The adventitia was thickened, consisting entirely of dense bands of fibrous connective tissue.

The myocardium of the auricles showed a degeneration of some of the muscle fibers and a slight amount of brownish pigmentation in the cytoplasm of the cells. Short bands of fibrous tissue lay between the muscle fibers and in

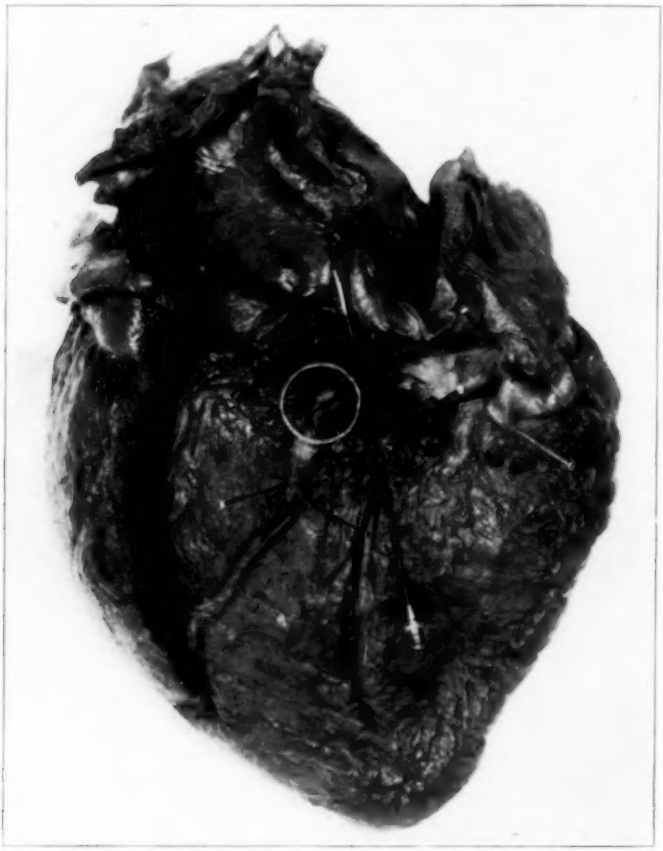

Fig. 4.—Heart showing tortuous and sclerosed anterior coronary artery. At the point enclosed by the circle, the lumen was practically occluded by a calcareous plaque.

places in which degeneration had taken place. The ventricles, especially the left, showed diffuse degenerative changes and marked fibrosis. In the region below the occlusion of the anterior coronary artery, the muscle cells appeared to be almost completely displaced by connective tissue. The cytoplasm of the remaining muscle cells showed a brown granular deposit. The vessel walls were quite thick and sclerosed throughout.

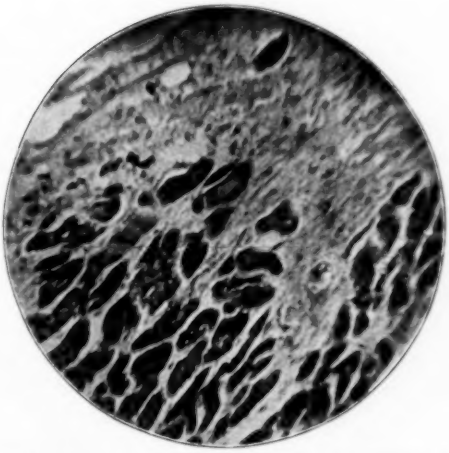

Fig. 5.—Photomicrograph of a section of the left ventricle below the point of occlusion of the anterior coronary artery, showing marked fibrosis and replacement of muscle cells by connective tissue.

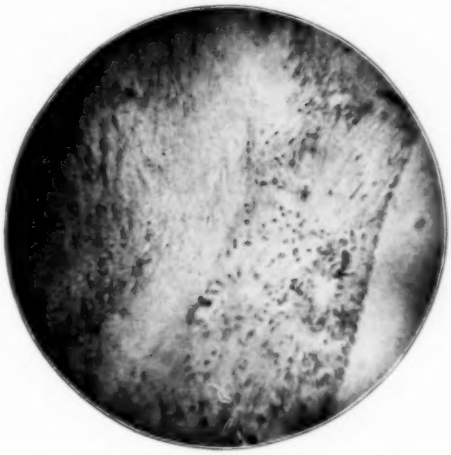

Fig. 6.—Photomicrograph of the anterior coronary artery, showing a marked calcareous deposit with thickening of the intima and with fibrosis.

The diagnosis was arteriosclerosis of the coronary arteries with complete occlusion of the descending branch of the left anterior by calcareous plaques, 11 cm. from its origin; sclerosis of the right posterior with partial occlusion of the descending branch, 5 cm. from its origin; marked hypertrophy of the heart associated with chronic interstitial myocarditis and brown atrophy, and atheromatous changes in the pulmonary artery and bulbus aortae.

COMMENT

It would appear, in view of the postmortem findings in this case, that the inversion of the T-waves in Leads I and II and the widening of the Q-R-S group were the result of grave myocardial disease, and that their persistence justified one in giving a grave prognosis.

SUMMARY

1. The ability of the clinician to diagnose valvular disease of the heart and lesions of the conductive system is well established.

2. If data can be obtained whereby we can more frequently detect myocardial damage, a more accurate prognosis can be made.

3. Evidence has been accumulating that electrocardiograms showing persistent straddling or splitting of the Q-R-S complex and inversion of the T-waves in Leads I and II are indicative of myocardial damage.

4. A case is reported in which electrocardiograms were obtained illustrating the presence of a prolonged Q-R-S complex, notching of the S-wave in Lead II and inversion of the T-wave in Leads I and II. A diagnosis of damaged myocardium was made and a bad prognosis given. Sudden death of the patient occurred within four months and postmortem examination of the heart revealed chronic interstitial myocarditis and marked coronary sclerosis, with occlusion of the descending branch of the left anterior coronary artery.

5. The association of the foregoing normalities of the electrocardiogram with definite myocardial and coronary damage, with resulting early death, appears to strengthen the belief that these findings justify a bad prognosis, particularly if they persist.

6. These abnormalities of the electrocardiogram are usually accompanied by other signs of a failing myocardium, but in certain cases may be the only evidence demonstrable.

EXPERIMENTAL INFECTIOUS STREPTOCOCCUS ENDOCARDITIS AND ITS ARSENICAL THERAPY (SODIUM CACODYLATE) *

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Definition
Etiology
Experimental Observations by Others
Mortality Reports
Specific Therapy
Animal Experimentation
(*a*) Production of Endocarditis
1. Methods
2. Results
(*b*) Arsenical Therapy
1. Methods
2. Results
Discussion
Conclusions

DEFINITION

Names have been introduced at various times descriptive of the pathologic changes occurring in heart valves following bacterial infections. Such names as simple acute endocarditis, benign, infectious, bacterial, chronic, malignant, septic and ulcerative endocarditis and more recently endocarditis lenta and subacute bacterial endocarditis have been suggested by clinicians. Litten,[1] in 1900, classified infections of the heart valves into acute, malignant and chronic, by the first two meaning infections causing in patients severe septic symptoms and death in a short time, by the last one mentioned those less severe and of much longer duration. Litten's classification prompted a lively discussion regarding septic or malignant endocarditis referred to by the early writers. Simons [2] prefers the term "bacterial endocarditis," a designation more accurate than "malignant," "septic" or "ulcerative." Libman [3] prefers the names "subacute bacterial endocarditis" (replacing the word "bacterial" by "streptococcus" or the name of such other organism as may be the causal agent) for all such infections continuing at least six weeks. The clinical designation of this disease seems to be

* Work done in the Pathological Laboratory of St. Luke's Hospital.

1. Berl. klin. Wchnschr. **36**:609, 1899.
2. Quart. J. Med. **7**:291, 1914.
3. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

best expressed by the terms "subacute" or "chronic infectious endocarditis," and where the causal bacterium has been demonstrated, its specific relation expressed by including in the name a significant term; for example, chronic infectious streptococcus endocarditis.

ETIOLOGY

Virchow,[4] in 1855, suggested the etiologic relationship between bacterial infections of the uterus and valvular endocarditis. This is the first mention of a sequence of infections which now generally is believed to exist; that is, valvular endocarditis is secondary to some primary focus of infection elsewhere in the body. A series of reports between 1887 and 1899 by Weischelbaum,[5] Frankel,[6] Sanger and Harbitz [7] mention the specific bacteria associated with malignant or septic endocarditis and include streptococci, staphylococci, and gonococci. By developing methods and technic for culturing the blood of patients, Sittman [8] thoroughly established this aid in diagnosing chronic infectious endocarditis, although previous sporadic attempts had been made by others to culture bacteria from the blood of patients suspected of having endocarditis. Later refinements by Kraus,[9] Gravitz,[10] Kuehnau,[11] Lænhartz [12] and Canon [13] further emphasized the importance of culturing the blood.

Although bacteria such as streptococci, staphylococci, gonococci, pneumococci, Friedländer's bacillus and *Bacillus influenzae* have been isolated from the blood of patients with endocarditis and also from the diseased heart valves at postmortem, the organism most frequently found in such infections is a coccus, variously termed *Streptococcus viridans, Streptococcus mitis, Streptococcus tenuans* or simply an endocarditis coccus. Some clinicians such as Simons [2] and Billings,[14] choose to place the organism in the streptococcus-pneumococcus group without further classification. All observers agree that the organism is a gram-positive coccus of low virulence, producing green on human blood agar and at some time growing in chains.

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4. Virchow: Gesammelte Abhandlungen, 1855.
5. Weischelbaum: Centralbl. f. Bakteriol. **2**:209, 1887.
6. Frankel: Virchows Arch. f. path. Anat. u. Physiol. **108**:286, 1887.
7. Sanger and Harbitz: Deutsch. med. Wchnschr. **25**:121, 1899.
8. Sittman: Deutsch. Arch. f. klin. Med. **53**:323, 1894.
9. Kraus: Wien. klin. Wchnschr. **8**:472, 1895.
10. Gravitz: Charité-Ann. **19**:154, 1894.
11. Kuehnau: Ztschr. f. Hyg. u. Infektionskrankh. **25**:492, 1897.
12. Lænhartz: München. med. Wchnschr. **48**:1123 and 1157, 1901.
13. Canon: Mittheilungen aus den Grenzgebieten **10**:411, 1902.
14. Billings, F.: Chronic Infectious Endocarditis, Arch. Int. Med. **4**:409 (Nov.) 1909.

EXPERIMENTAL OBSERVATION BY OTHERS

Experimental studies of heart valve infections are comparatively few, clinical references many. In 1914, Simons [2] published an excellent review of the clinical literature up to that time, and in 1917 Kinsella [15] published a similar review including nearly all of Simon's references.

In 1885 a chronic septicemia was produced experimentally for the first time by Philopowicz and Wyssokowitch.[16] They found an endocarditis in rabbits after the intravenous injection of pure cultures of bacteria. Wyssokowitch [16] observed such infections frequently if he injured the heart valves or endocardium by sounding one of the carotid arteries before the intravenous injection of bacteria. In the same year, Ribbert [17] produced tricuspid endocarditis by the injection of bacterial suspensions prepared from growth on potato medium. Numerous attempts have been made to discover the fate of bacteria injected intravenously into animals, beginning as early as 1874 with the experiments of Traube and Gescheidlen.[18] Bull,[19] seems to express best the essential results of such experiments. He believes the virulence of bacteria (streptococci and pneumococci) injected intravenously determines the fate of the host. If the streptococci are virulent, the animal (rabbit) dies within six days, whereas a less virulent strain produces a chronic infection somewhere in the body.

Allison [20] produced streptococcus septicemia in forty-six rabbits with *Streptococcus hemolyticus* and *Streptococcus viridans* recovered from patients with puerperal sepsis, mastoiditis, from normal and infected throats and from patients with other diseases in which bacteria were present in the blood. He found in these experiments that the course of such septicemias, experimentally produced, depends on several factors, such as the virulence of the bacteria injected, the native agglutinating power of the rabbit serum and the phagocytic property of the leukocytes. If the organisms are not virulent enough to cause death at once or within a few hours after injection, they disappear rapidly from the circulating blood and accumulate in the capillaries and venous sinuses of the viscera. After a time the bacteria reappear in the circulation and cause a rapidly fatal septicemia or localize in some organ from which repeated "showers" of bacteria appear in the blood stream.

15. Kinsella, R. A.: Bacteriologic Studies in Subacute Streptococcus Endocarditis, Arch. Int. Med. **19**:367 (March) 1917.
16. Philopowicz and Wyssokowitch: Ztschr. f. Hyg. u. Infectionskrankh. **1**:3, 1886.
17. Ribbert: Deutsch. med. Wchnschr. **11**:717, 1885.
18. Traube and Gescheidlen: Jahresbericht d. Schlessischen Gesellsch. f. Vaterland. Culture, 1874.
19. Bull: J. Exper. M. **22**:475, 1915.
20. Allison: J. M. Res. **38**:55, 1918.

When tissue reactions are sufficient to combat the bacteria the animal slowly recovers.

Rosenow [21] has emphasized that many bacteria localize specifically in certain tissues of the body, and such terms as "specificity," "selective action" or "elective activity" have been suggested to designate this affinity.

In an effort to find some drug which might be efficacious in the treatment of valvular endocarditis, Allison [20] used experimentally arsenical preparations, such as different brands of arsphenamin. He observed that the mortality in rabbits with experimental septicemias treated with these arsenicals was 30 per cent. less than a corresponding group which received no treatment.

MORTALITY REPORTS

The death rate of patients with chronic infectious endocarditis is high. Osler,[22] reporting the clinical results of ten patients, mentions a 100 per cent. mortality. Billings [14] observed one of fourteen patients recover, Horder [23] one of 150, and Libman [24] five of 146. Libman's five patients when mentioned in a report in 1923 had been well nine, seven, five and two years, respectively. Oille, Graham and Detweiller,[25] have reported a series of twenty-three patients with positive blood cultures and a diagnosis of "subacute bacterial endocarditis" in which they gave a hopeful prognosis, but as none of these patients had been followed for more than a year, and since the disease is chronic it is presumptive to record them as having recovered.

Clinicians usually regard this disease as fatal.

SPECIFIC THERAPY

Numerous attempts have been made to find a specific therapy for active infectious endocarditis. Autogenous vaccines, serums, blood transfusions, and drugs introduced into the system for the purpose of destroying or attenuating the bacteria have been tried. Horder,[23] in a large experience, has failed to observe any benefit from serums and blood antiseptics.

Autogenous vaccines and antistreptococcic serums have been used extensively by Billings [14] and Jochmann,[26] but with no definite results.

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21. Rosenow: J. Infect. Dis. **6**:245, 1909; **7**:411, 1910; **11**:210, 1912; New York State M. J. **12**:441, 1912.
22. Osler: Quart. J. Med. **11**:219, 1909.
23. Horder: Quart. J. Med. **11**:289, 1909.
24. Am. J. M. Sc. **144**:313 (Sept.) 1912. Also Footnote 3.
25. Oille, J. A.; Graham, D., and Detweiller, H. K.: Streptococcus Bacteremia in Endocarditis: Its Presence Before and During the Development of Endocardial Signs, J. A. M. A. **65**:1159 (Oct. 2) 1915.
26. Jochmann: Berl. klin. Wchnschr. **49**:436, 1912.

Various antiseptics have been injected intravenously, such as collargol and eusol, in the hope of establishing some specific therapeutic agent. Arsenic in various forms has been used but in no systematic way. Recently Capps [27] reported the clinical progress of eight patients with *Streptococcus viridans* endocarditis treated by the intravenous injection of sodium cacodylate. Four of these patients were apparently well after three, five, six and twelve years, respectively, which affords

Fig. 1.—An extensive thrombo-ulcerative aortic endocarditis.

some hope from arsenical therapy. Since his first report, Billings has also had several patients who recovered under treatment with sodium cacodylate.

Sodium cacodylate has been given in various diseases, usually by mouth, but also hypodermically and intravenously. Peyre [28] has

27. Capps: Am. J. Md. Sc. **40**:165 (Jan.) 1923.
28. Peyre: Presse méd. **27**:615, 1919.

reported the results of forty patients with recurrent fever whom he had treated with sodium cacodylate given intravenously, saying that it did not replace arsphenamin in this disease but was efficacious and without the bad effects sometimes occurring with arsphenamin.

Sodium cacodylate is the dimethylarsenate of sodium containing a variable amount of water of crystallization (usually about 30 per cent.) $Na\ (CH_3)_2\ AsO_2$. Roasenda [29] ascribes its low toxicity to the fact

Fig. 2.—A thrombo-ulcerative mitral endocarditis.

that it does not dissociate, and the effects are obtained by partial reduction, decompositions and transformations (probably oxidations) when in contact with tissue fluids.

ANIMAL EXPERIMENTATION

The observations recorded here concern: (1) the production of endocarditis in animals by the injection of strains of *Streptococcus viridans* obtained by blood cultures from patients suffering from chronic

29. Roasenda: Policlinico (Sez. Prat.) **27**:826 (Aug. 2) 1920.

infectious endocarditis; (*2*) the influence of sodium cacodylate on the clinical course and the healing process of endocardial infections in rabbits.

Methods.—Various methods of blood culture were employed. Rosenow's [30] anaerobic tubes were used constantly, modified slightly, using an 0.8 per cent. agar and ascitic fluid with the sediment of blood centrifuged at high speed and sealed with paraffin. The tubes were controlled by plates of the same materials. The modification of the

Fig. 3.—An extensive thrombo-ulcerative tricuspid and mural endocarditis.

Rosenow tubes consisted in using a tall tube, plugged with cotton at one end and a cork stopper at the other, the advantage being that the tube need not be broken to remove colonies of bacteria from the column of agar. The Noguchi [31] anerobic tubes with a 0.5 per cent. agar and citrated blood to fill half of a tube and when solidified covered by the same quantity of Ringer's solution, blood serum and

30. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Special Methods, J. A. M. A. **63**:903 (Sept. 12) 1914.

31. Noguchi: J. Exper. M. **27**:575, 1918; **16**:191, 1912; **30**:13, 1919.

blood, were used at times. Detweiler's[32] modification of Rosenow's method in which the centrifuged blood sediment is incubated in bouillon for twenty-four hours and then planted according to the Rosenow method proved satisfactory. Blood agar plates were made at the bedside, the layer of blood agar covered by another layer of agar, this by melted paraffin and the plates and bouillon tubes taken immediately to the incubator. Holman's[33] serum sugar broth was used in making cultures of the supernatant blood serum, and all the streptococci were

Fig. 4.—A small vegetation of the endocardium of the mitral valve (×170).

classified according to their sugar-fermentation reactions. All mediums were titrated colorimetrically to a p_H 7.6. Approximately 35 c.c. of blood were withdrawn from the median cubital vein of patients.

Of forty-four patients of Drs. A. R. Elliott, R. B. Preble, N. C. Gilbert, J. L. Miller and J. A. Capps at St. Luke's Hospital and several on the service of Dr. Capps at the Cook County Hospital and a few of

32. Detweiler, H. K., and Robinson, W. L.: Experimental Endocarditis. J. A. M. A. **67**:1653 (Dec. 2) 1916.
33. Holman: J. M. Res. **34**:377, 1916.

his patients outside of hospitals in whom a subacute or chronic bacterial or infectious endocarditis was diagnosed, a positive blood culture of *Streptococcus viridans* was obtained in thirty-five, an alphahemolytic streptococcus (Brown) in two, a total of thirty-seven, or 84 per cent., during the year.

Rabbits weighing approximately from (1.8 kg. to 2.2 kg.) 4 to 5 pounds and apparently in good health were selected. Salt solution suspensions of *Streptococcus viridans* cultures, forty-eight hours old, grown on human blood agar slants, were injected into the marginal ear vein and intracardially, and the animals carefully watched, cultures made from their blood at intervals of several weeks under aseptic precautions by introducing a large needle into the ear vein of the rabbit and

Fig. 5.—A small portion of the vegetation of Fig. 1 demonstrating the bacteria (×1200).

catching the blood drops in Petri dishes. The cultures of the blood were made as described. Leukocyte counts were made at intervals and the general condition of the rabbit observed. (The introduction of the needle into the ear vein is an easy procedure and serves as a much more efficacious means of drawing blood than the usual method of cutting the marginal ear vein of the rabbit with a razor.)

The report of endocarditis produced includes only such as were proved by postmortem examination.

Results.—Of fifty-three rabbits injected, forty-six have either died or have been killed and an endocarditis or pericarditis or both has been demonstrated in thirty-eight, and of the thirty-eight an endocarditis in thirty-five, or a total of almost 80 per cent. Table 1 illustrates the occurrence of an endocarditis in ten rabbits, serving as controls for

the ten of Table 2 to be discussed later. The animals were weighed approximately every two weeks.

(2) Arsenical Therapy.

These experiments were carried out to determine the effect of sodium cacodylate on the clinical course of an endocarditis in rabbits.

Methods.—Distilled water solutions of sodium cacodylate (Mallinckrodt, U.S.P.) were injected into the marginal ear vein of rabbits in doses of from one-half a grain to 3 grains a day, for periods vary-

Fig. 6.—An extensive aortic endocarditis.

ing from two weeks to ten weeks. It is generally believed among clinicians that the peculiar odor of the patients' excreta, an odor resembling garlic, is evidence of the potency of the sodium cacodylate. This odor was used as a criterion for increasing the dose of the drug in the rabbits. Cultures of the blood were made approximately every two weeks. The rabbits listed in Table 2 were carefully observed for clinical endocarditis or its complications. In a small percentage of the animals an arthritis of the feet developed. When an endocarditis was demonstrated by positive blood culture the injections of sodium cacodylate were begun.

In several animals, the injection of cacodylate was begun immediately after the injection of the suspensions of *Streptococcus viridans*.

In other animals, a series of cacodylate injections was given, followed by huge or as near as possible lethal doses of *Streptococcus viridans*. An equal number of rabbits received the same size of streptococcus suspensions. Still others received a series of cacodylate injections followed by a smaller suspension of *Streptococcus viridans*, not enough to kill if possible. A corresponding number again received

Fig. 7.—A healing mitral endocarditis (note the granulation tissue).

the streptococcus suspensions alone. This series had the injection of streptococci repeated three days after the first injection, each time preceding the streptococcus injections by a rather large dose of cacodylate in one-half of the animals.

Results.—In Table 1 are collected the results of the injection of suspensions of streptococci with the development of an endocarditis. Urine obtained at postmortem contained at times erythrocytes and albumin indicating renal infection and at others casts and albumin alone. The valvular changes illustrated are of an aortic (Fig. 1), a

TABLE 1.—*Illustrating the Development of Endocarditis in Ten Rabbits*

Rabbit	Weight in Pounds	Strain of Streptococcus	Date of Injection	Amount Injected, Normal Saline Suspensions	Blood Cultures	Date of Death	Postmortem Findings	Remarks
10	9/11/22, 4 10/ 2/22, 3.7	Rx	9/11/22	The washings of 2 blood agar slants	5 positive during life; many colonies at necropsy	10/ 2/22	Extensive thrombo-ulcerative tricuspid endocarditis; generalized anasarca; fibrinopurulent pericarditis	Severe arthritis of the right front foot 4 days after injection; progressive emaciation
11	10/12/22, 4.2 10/25/22, 3.9 12/ 6/22, 5.37 12/26/22, 3.5	W_1	10/12/22	The washings of 3 blood agar slants	1 negative 10/12/22, 1 positive 11/12/22, necropsy positive	12/26/22	Vegetative aortic and tricuspid endocarditis; multiple subcapsular renal hemorrhages	Severe chill shortly after the first injection
12	12/29/22, 3.87 1/ 8/23, 3.5	S_2	12/29/22	The washings of 2 blood agar slants	150 colonies on one plate, 12/30/22; many colonies at death	1/ 8/23	Fresh thrombo-ulcerative mitral endocarditis (mitral stenosis); fresh infarcts of the kidneys; marked hyperplasia of the spleen	Severe chill at the time of injection; a rapid, septic course
13	12/29/22, 5.75 1/22/23, 5.5 3/16/23, 5.7 3/19/23, 5	W_3	12/29/22	The washings of 4 blood agar slants	2 positive and 1 negative during life; many colonies at necropsy	4/19/23	Fresh thrombo-ulcerative tricuspid and mural endocarditis; emboli abscesses of the right lung; healed fibrous pericarditis	Urine, large amount of albumin; Streptococcus viridans recovered from lung abscesses
14	2/20/23, 4 3/17/23, 2.62	W_5	2/24/23	The washings of 6 blood agar slants	1 positive during life; many colonies at necropsy	3/17/23	Huge mural thrombo-ulcerative endocarditis of the right auricle and the tricuspid valve; passive hyperemia of the lungs	Urine, a few erythrocytes and a trace of albumin; progressive, rapid emaciation after the first week
15	2/20/23, 5.37 3/ 2/23, 5	N_2	2/24/23	The washings of 5 blood agar slants	1 positive during life; many colonies at necropsy	3/ 2/23	Acute vegetative mitral endocarditis; multiple subpleural and renal subcapsular hemorrhages; acute hyperplasia of the spleen	Urine, a moderate amount of albumin; few erythrocytes
16	3/27/23, 5.44 4/30/23, 4.37	N_2	3/28/23	The washings of 8 blood agar slants	Many colonies at necropsy	4/30/23	Healing thrombo-ulcerative tricuspid endocarditis; multiple subpleural hemorrhages	Urine, very many epithelial cells
17	3/20/23, 5 3/26/23, 5.5	W_3	3/26/23	The washings of 8 blood agar slants	Many colonies at necropsy	3/28/23	Acute thrombo-ulcerative mitral endocarditis; multiple renal infarcts; embolic lobar pneumonia (R. L. L.)	Rapid septic course of 2 days; urine, trace of albumin, few erythrocytes, many renal epithelial cells
18	3/10/23, 4.37 3/30/23, 3.75 5/ 3/23, 3	N_2	3/10/23	The washings of 6 blood agar slants	1 positive during life; positive at necropsy	5/ 3/23	Fresh mural thrombo-ulcerative endocarditis of the right auricle; moderate ascites	April 1, arthritis of the left front foot, listlessness; loss of weight; urine, small amount of albumin and erythrocytes
19	3/10/23, 4.75 3/30/23, 4.25 3/ 3/23, 3.25	C_1	3/10/23	The washings of 6 blood agar slants	1 positive during life; positive at necropsy	5/ 3/23	Slight acute vegetative aortic endocarditis	Arthritis of the right front foot shortly before death; urine, trace of albumin

TABLE 2.—*Illustrating the Results Obtained with Ten Rabbits Receiving Sodium Cacodylate Intravenously*

TABLE 2.—*Illustrating the Results Obtained with Ten Rabbits Receiving Sodium Cacodylate Intravenously*

Rabbit	Weight in Pounds at Intervals	Date of Injection of Streptococci	Amount Injected; Saline Suspensions	Blood Culture Positive	Leukocyte Counts at Intervals	Cacodylate; Date of First Dose	Total Cacodylate of Soda	Date and Manner of Death	Urine at Necropsy	Postmortem Findings	Remarks
101	9/23/22, 4 10/23/22, 3.62	9/23/22	The washings of 3 blood agar slants	1	7,000, 9/23/22; 6,100, 10/4/22	½ grain 10/8/22	16 grains in 6 weeks	11/12/22; killed with ether	Bladder empty	Recent tricuspid and mitral thrombo-ulcerative endocarditis; fibrous mitral endocarditis; fresh infarct of the right lung	Strong "garlic odor" Oct. 18; arthritis of the front feet, marked anemia, noted during disease
102	9/21/22 to 12/20/22, 4.94, 4.7, 5.12	9/21/22	The washings of 3 blood agar slants	2	8,000, 9/21/22; 9,900, 9/25/22; 7,800, 10/4/22 11,500, 1/18/23	½ grain 10/6/22	16 grains in 6 weeks	12/20/22; killed with ether	Bladder empty	Recent thrombo-ulcerative mitral endocarditis; healed fibrous tricuspid and mitral endocarditis; multiple subpleural hemorrhages	In the recent valve lesion, there were many cocci; "garlic odor" as above
103	12/29/22, 3.62; Jan. 1923, 3.75, 3.75, 3.16	12/29/22	The washings of 3 blood agar slants	3	11,500, 1/18/23	½ grain 1/11/23	11 grains in 2 weeks	1/23/23; died	Trace of albumin, erythrocytes	Slight serofibrinous and fibrous pericarditis; slight fresh tricuspid endocarditis; healed mitral endocarditis; slight ascites	The blood culture at postmortem grew many gram-positive green producing cocci; probably reinfection
104	12/29/22, 6.16; Jan. 1923, 6.25, 5.87, 6 Jan., 1923	12/29/22 and 1/10/23	(1) The washings of 3 (2) of 2 blood agar slants	2	10,800, 1/18/23	½ grain 1/10/23	15 grains in 2 weeks	1/24/23; killed with ether	Albumin; few erythrocytes	Huge fibrinopurulent pericarditis (Cor villosum), and slight fibrous pericarditis; compression atelectasis of the lungs	The pericardial sac filled nine-tenths of the chest cavity; "garlic odor" of its content was strong
105	12/29/22, 5.62; Jan. 1923, 5.62, 5.87, 5.62, 6.16	12/29/22	The washings of 3 blood agar slants	1	8,000, 1/18/23; 11,400,	½ grain 1/8/23	14 grains in 2 weeks	1/31/23; killed with ether	Albumin; few erythrocytes	Healing fibrous and fibrinous pericarditis; multiple subepicardial hemorrhages; hyperplasia of the spleen	Very large spleen; the animal seemed entirely well when killed
106	12/29/22, 3.87; Jan. and Feb., 4.37, 4.44, 4.62, 5.62	12/29/22	The washings of 3 blood agar slants	3	9,500, 1/18/23; 9,200, 1/29/23	½ grain 1/8/23	18 grains in 3 weeks	2/6/23; killed with ether	Bladder empty	Healed fibrous aortic endocarditis; marked obliterative fibrous pericarditis	No bacteria grew in a blood culture at postmortem
107	10/12/22, 5.5 10/23/22, 5.4 12/ 6/22, 6.5 1/11/23, 5.4 2/ 7/23, 6.37	10/12/22	The washings of 3 blood agar slants	2	9,600, 1/29/23	½ grain 1/13/23	40 grains in 4 series of 2 weeks each	2/7/23; killed with ether	Clear urine, no albumin or red cells	Healed fibrous and localized fibrinous pericarditis; healed right mural endocarditis; hypostatic hyperemia of the lungs	Animal sick in October, apparently better in November and sick in January, and became well the last 2 weeks of January
108	2/20/23, 6.5 3/ 6/23, 6.75 3/19/23, 7 4/ 2/23, 4.5	2/24/23	The washings of 6 blood agar slants	1 (neg. culture at necropsy)	8,800, 2/22/23	1 grain 2/27/23	31 grains in 2 weeks	4/2/23; died	Scanty; Many hyaline casts albumin	Recent thrombo-ulcerative tricuspid endocarditis; complete infarction of the lower lobe of the right lung; acute nephritis	Moderate salivation on the last day of the cacodylate injection
109	2/20/23, 5.2 3/ 6/23, 4.75 3/14/23, 4	2/24/23	The washings of 6 blood agar slants	1	14,000, 2/22/23	1 grain 2/27/23	14 grains in 2 weeks	3/14/23; died	Bladder empty	Fresh thrombo-ulcerative mural endocarditis of both auricles; healing pericarditis; bronchopneumonia	March 7, animal became more listless, and March 11 began to froth and have diarrhea
110	2/20/23, 6.4 3/ 6/23, 7 3/19/23, 7.2 4/ 3/23, 6.2	2/24/23	The washings of 6 blood agar slants	2	9,000, 2/22/23	1 grain 2/27/23	29 grains in 2 weeks	4/3/23 died	Albumin; granular casts, erythrocytes	Mural thrombo-ulcerative tricuspid endocarditis; embolic (?) lobar pneumonia, R. U. L. and R. M. L.; healed fibrous pericarditis	Up to the last week the animal seemed to be doing well; pneumonia apparently killed him

mitral, (Fig. 2) and a tricuspid (Fig. 3) endocarditis, of which there were many demonstrated.

The extent of the endocarditis varied; with some animals there was almost a complete stenosis of the valve, while others had only a few vegetations. Gross lesions were examined microscopically, except a few in which section would have destroyed a tissue otherwise valuable for gross demonstration. The tissues were stained for bacteria by the Goodpasture[34] method, and in many of the endocardial vegetations diplococci and cocci in short chains were demonstrated.

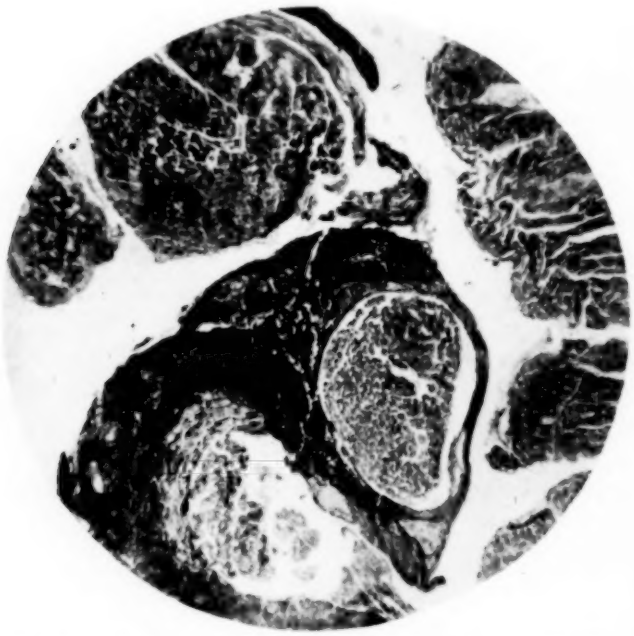

Fig. 8.—A further organized clot of the tricuspid valve (×60).

In Table 2 are collected the results of the injection of ten rabbits with sodium cacodylate after an endocarditis had been demonstrated by blood culture. Six were killed with ether one to two months after their injection with streptococci, at which time they had apparently recovered from the infection. Four died. The postmortem changes were those of an endocarditis, active, healing or healed, or a pericarditis. The figures in the "Blood Culture" column indicate the number of times a positive culture was obtained during life.

34. Goodpasture: Medical War Manual, No. 6, 1919, p. 349.

TABLE 3.—*Results of Injection of Sodium Cacodylate Followed by Huge Doses of Normal Saline Suspensions of Streptococcus Viridans—42, 44, 49 and 51 Being Controls*

Rabbit	Weight in Pounds	Sodium Cacodylate Injected	Strain of Streptococcus	Amount of Saline Suspension Injected	Length of Life After Injection	Postmortem Findings
41	5.5	17 grains, 2 grains first day, then 3 gr. daily for 5 days	M_2	The washings of 8 blood agar slants	65 days	Slight mural endocarditis of the left auricle and right ventricle (partial calcification); healing renal infarcts
42	5.62	None	M_2	The washings of 8 blood agar slants	8 days	Extensive thrombo-ulcerative aortic endocarditis; multiple renal infarcts; huge hyperplasia of spleen
43	6	6 grains; 3 grains daily for 2 days	W_3	The washings of 10 blood agar slants	30 hours	Fibrinopurulent pericarditis; bronchopneumonia; bilateral pleuritis
44	4.75	None	W_3	The washings of 10 blood agar slants	20 hours	Mural thrombo-ulcerative right and left endocarditis; multiple subcapsular renal hemorrhages
48	6	6 grains; 3 grains daily for 2 days	M_3	The washings of 10 blood agar slants	11 days	Huge thrombo-ulcerative (verrucous) aortic endocarditis; multiple renal infarcts
49	5.25	None	M_3	The washings of 10 blood agar slants	4 days	Thrombo-ulcerative mitral (vegetative) endocarditis; slight ascites; marked passive hyperemia of the liver
50	5.75	6 grains; 5 grains daily for 2 days	B_2	The washings of 10 blood agar slants	72 hours	Multiple subendocardial hemorrhages of the right auricle; renal infarcts; fibrinous pericarditis
51	5.37	None	B_2	The washings of 10 blood agar slants	Less than 20 hours	Thrombo-ulcerative (vegetative) mitral and tricuspid endocarditis; complete infarct of one lung lobe

TABLE 4.—*Results Obtained with Two Rabbits Given Cacodylate Immediately After Injecting Streptococci and for Weeks Thereafter*

Rabbit	Weight in Pounds at Intervals	Strain of Streptococcus	Amount of Streptococcus Injected and Date	Blood Culture	Sodium Cacodylate (1) Initial Dose (2) Total (3) Time	Date Killed	Postmortem Findings
111	4.3, 4.1, October	W_4	Washings of 3 blood agar slants 10/12/22	Two cultures negative 2 weeks apart	(1) ½ grain 10/13/22 (2) 15.25 grains (3) 5 weeks	11/18/22	No changes of any of the organs
112	4.3, 4.1, 10/12/22; 5.7, 5.6, 2/20/23	S_1	Same as 111	Culture negative 10/18 and 11/2/22, 1/17 and 1/29/23 (4)	(1) ½ grain 10/13/22 (2) 45 grains (3) Oct. 13 to Jan. 31 with intervals of rest	2/20/23	Small fibrous tag of the pericardium; healed renal infarcts

The photomicrographs illustrate various stages of the endocarditis, from a small endocardial vegetation to an extensive thrombo-ulcerative endocarditis (4, 5 and 6), and from a healing mitral to a healed fibrous endocarditis (Figs. 7, 8 and 9).

In Table 4, two rabbits illustrate results with the injection of suspensions of *Streptococcus viridans* followed the day after by an injection of a small dose of cacodylate, and for several months thereafter. At necropsy, in one, two, in the other, four months after the injection of the streptococcus, when they seemed well, no heart changes were noted, but in the latter several scars of renal infarcts were demonstrated.

Fig. 9.—A completely healed fibrous mitral endocarditis (×135).

When the rabbits were injected with rather large doses of cacodylate followed by huge suspensions of *Streptococcus viridans*, the results represented by Table 3 are noteworthy in that in each case the animal receiving the cacodylate before the streptococcus lived longer than the control which received no cacodylate. Rabbit 41, receiving the longest course, died seventy days after injection with the streptococcus, while the control rabbit died eight days after injection. In the other six, the difference was not as marked, yet distinct.

TABLE 5.—*The Results of Repeated Injections of Streptococcus Viridans Preceded by Injections of Sodium Cacodylate, 53, 55, 57, 59 and 61 Serving as Controls*

Rabbit	Weight in Pounds at Intervals	Amount of Sodium Cacodylate and the Date of Injection	Amount of Saline Suspension of Streptococcus Viridans	Sodium Cacodylate Repeated Streptococcus Injection Repeated	Length of Life After First Injection	Postmortem Findings
52	May 19, 3.3 May 24, 3.3 May 29, 3.2 June 8, 2.75	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Alive and in good condition 20 days	
53	May 19, 4.5 May 24, 4 May 29, 3.7 June 4, 3.3	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, June 4, 1923	Multiple subpericardial and pulmonary abscesses; slight serofibrinous pericarditis; acute hyperplasia of the spleen
54	May 19, 4 May 24, 3.8 May 29, 3.3 June 8, 2.8	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Alive and in good condition 20 days	
55	May 19, 4 May 24, 3.75	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 25, 1923	Slight fresh thrombo-ulcerative mitral endocarditis; slight fibrinous pericarditis
56	May 19, 3.62	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	.....	Died, May 23, 1923	Bilateral hemothorax; marked edema and hyperemia of the lungs; slight fresh thrombo-ulcerative endocarditis
57	May 19, 3.5 May 24, 3.5	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 28, 1923	Extensive thrombo-ulcerative tricuspid endocarditis; serofibrinous pericarditis and bilateral pleuritis
58	May 19, 3.3 May 24, 2.8 May 29, 2.2 May 31, 1.9	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Died, May 31, 1923	Recent thrombo-ulcerative mitral and mural endocarditis; multiple healing infarcts of the kidneys; fibrinous pleuritis
59	May 19, 3.3 May 24, 2.8	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, May 26, 1923	Extensive thrombo-ulcerative (verrucous) tricuspid endocarditis
60	May 19, 3.5 May 24, 3.2 May 29, 2.8 June 8, 2	May 19, 3 grains May 20, 3 grains May 21, 3 grains	The washings of 3 blood agar slants several seconds after the cacodylate, May 21, 1923	May 24, 2 grains followed by the washings of 1 blood agar slant	Died, June 8, 1923	No evidence of endocardial infection; the only gross finding, marked emaciation
61	May 19, 4.3 May 24, 4.2 May 29, 3.6 June 8, 2.8	None	The washings of 3 blood agar slants, May 21, 1923	The washings of 1 blood agar slant, May 24	Died, June 9, 1923	Thrombo-ulcerative tricuspid and mural endocarditis; healing lung infarcts; fresh splenic infarct

The ten rabbits of Table 5 illustrate results similar to those of Table 3, but here a smaller suspension of streptococci was injected and another small suspension injected three days later, in five a course of cacodylate being given for several days and a single injection of cacodylate immediately before each injection of streptococci and in the other five only the streptococci. Four of the controls died soon, one of the animals receiving the cacodylate died five days after the control, receiving no cacodylate, and the other died two days after its initial injection from an extensive hemothorax and a slight tricuspid endocarditis. The other two rabbits receiving the cacodylate are still living and appear well. The fifth control died twenty days after injection with the streptococci.

Of the other animals not mentioned in the tables, some died of an endocarditis or a pericarditis later. One developed a marked cystitis and pyelitis and died of pneumonia later. Others died of bites inflicted by their mates. One control animal seemed well and when killed four months later some ascites and a healed splenic infarct were demonstrable. Five of the fifty-three rabbits are still living.

The term thrombo-ulcerative is the generally recognized designation by pathologists of the endocardial lesions of chronic infectious endocarditis.

DISCUSSION

This report suggests possibilities for the specific therapy of valvular endocarditis. While the results obtained with forty-eight rabbits do not establish conclusively the value of sodium cacodylate therapy with chronic infectious endocarditis, yet they afford reasons for believing that it is of some value.

The "selective actions" or "elective activity" of *Streptococcus viridans* isolated from patients with endocardial lesions for the endocardium and pericardium of rabbits has been repeatedly demonstrated by Rosenow and others. The fact that 80 per cent. of rabbits injected developed such an endocarditis in this series seems to stress the "selective action" of this coccus. At times the endocarditis develops with remarkable rapidity, the shortest time noted being twenty hours. The rapidity of production of an endocarditis may be influenced by the virulence of the streptococci, the amount of the suspension injected, the weight of the animal, and its general condition and other factors not recognized at this time.

Animals receiving repeated injections of cacodylate first and then huge suspensions of streptococci seem to be better able to destroy the streptococci than those receiving no previous sodium cacodylate injections. It has been suggested by immunologists that such preparations as sodium cacodylate may have a protective influence for the host in

that they perhaps stimulate the endothelial cells of blood vessels and blood sinuses to greater phagocytosis.

CONCLUSIONS

1. In 84 per cent. of a group of patients in whom a chronic infectious endocarditis was suspected *Streptococcus viridans* was recovered by blood culture.

2. The essential needs for the isolation of *Streptococcus viridans* from the blood of patients during life seem to be anaerobic conditions, mediums rich in nutrient substances (liquid or solid), careful daily examinations of all mediums used for at least a week, and the withdrawal of a large quantity of blood (from 30 to 40 c.c.) at the proper time.

3. Sodium cacodylate seems to have some beneficial influence on the healing of heart valve infections.

4. Arsenical preparations, such as sodium cacodylate, may have a protective power for the endocardium or the pericardium.

THE COMPLICATIONS OF STAPHYLOCOCCUS FOCAL INFECTIONS*

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Ordinarily staphylococcic septicemias present a fulminating septic picture classically represented by repeated chills, fever, delirium, purpura, endocardial murmurs and multiple abscesses. The blood picture shows a leukocytosis and an anemia. Cocci are easily grown from the blood by the ordinary cultural methods. The infectious focus may be a minute pyogenic skin infection, a furuncle, a discharging ear or a suppurating sinus. Of these foci, the most important are the sources from the skin. Such a pyemic state is represented by generalized multiple abscesses of the organs, more particularly minute suppurative foci in the kidneys, heart muscle and lungs. Commonly the mitral and aortic valves show large thrombus masses with rapid destruction of the leaflets. The muscles, the medullary cavities of the long bones or joints may show collections of yellowish pus, from which cocci are readily grown. A pyemia which represents the acute type described can be experimentally simulated in rabbits by comparatively large intravenous injections of *Staphylococcus aureus*.

I do not care to emphasize this type, but that group of staphylococcus cases which is best represented by metastatic abscesses, commonly single, occasionally multiple, in various anatomic structures of the body. This group is representative of an intermittent blood stream infection from some focal origin, usually from boils, carbuncles, paronychia, impetigo or infected skin wounds. So striking is a history of a staphylococcus skin infection, succeeded at an unstated short interval of time by a clinical picture of perinephric abscess, unilateral suppurative nephritis or an acute osteomyelitis, and so constant are the cultural findings in the distant lesions compared with the primary focus, that the relationship of a focal skin infection to a metastatic internal lesion is given clinical proof.

Experimental, pathologic and clinical data regarding these focal skin associations with fairly constant metastatic lesions was first mentioned

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* From the medical department of the University of California Medical School.

* The reviewed cases were seen in the medical and pediatric services of the University Hospital and San Francisco Hospital. Drs. Moffitt, Lucas, Ebright, Kerr.

Operative procedures were performed in the surgical services of these hospitals; Drs. Brunn, Pope, Hinman, Baldwin.

in the continental literature. (Israel,[1] Rodet,[2] Lexer,[3] Jordan,[4] Schmitz,[5] Barth.[6]) More recently American observers have published clinical and experimental data which in no way refute, but augment such observations (Brewer,[7] Richardson,[8] McKenzie,[9] Phemister [10] and others).

For the past few years I have attempted to establish the portal of entry in cases of primary perirenal abscess; that is, abscesses which are not caused by continuity from adjoining diseased tissues. Cortical renal abscesses are the exception, however, and are not included, as the perirenal tissue is often involved by the outward extension of minute cortical collections of pus. The incidence of boils and carbuncles preceding such perirenal abscesses is high, and cultural methods yield *Staphylococcus aureus* from the evacuated pus in the majority of these cases. Similarly I have been interested in cases of muscle abscess, acute osteomyelitis and suppurative nephritis and their etiologic relationship to foci on the skin.

Recently, Phemister,[10] under the title of hematogenous staphylococcus infections secondary to foci in the skin, has grouped a series of cases similar to those reported below. He has reviewed the clinical and experimental literature from an authentic bibliography, and his cases exemplify his title clearly. I report these additional cases because it is felt such data will impress more thoroughly the etiologic and clinical facts so correctly intimated by his paper.

These cases are reviewed, with but four exceptions, from the records of the University of California Medical School. Two cases are taken from my notes during the recent war.

ACUTE UNILATERAL SUPPURATIVE NEPHRITIS

There is a difference of opinion as to which organism most frequently causes cortical abscess. Israel finds B. coli most frequent, but staphylococcus is a more common etiologic agent than the streptococcus, pneumococcus or the typhoid bacillus. There is some question as to whether the colon bacillus is a primary or secondary invader in many cases.

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1. Israel: Chir. Klin. d. Nierenkrankheiten, Berlin, 1901, p. 580.
2. Rodet: Rev. de Chir. **5**:272, 1885.
3. Lexer: Arch. f. klin. Chir. **53**:266, 1896.
4. Jordan: Chir. Congress, 1905, p. 18.
5. Schmitz: Centralbl. f. Bakteriol. **65**:259, 1912.
6. Barth: Arch. f. klin. Chir. **114**:477, 1920.
7. Brewer: Surg., Gynec. & Obst. 2:485, 1906.
8. Richardson: Surg., Gynec. & Obst. **21**:1, 1915.
9. McKenzie: Canadian M. A. J. **11**:714, 1921.
10. Phemister: Hematogenous Staphylococcus Infections Secondary to Foci in the Skin, J. A. M. A. **78**:480 (Feb. 18) 1922.

The condition may follow abscess formation in the skin at varying intervals of time. It is characteristic of micro-organisms in general, having gained entrance in the blood stream, to be excreted by the kidneys when not disposed of by the natural defenses of the host. The peculiarity of staphylococcus is that it grows ordinarily in clumps and clings together rather than spreads diffusely. These small groups lodge primarily in the glomeruli, and their pathogenicity calls forth abscess formation in the peripheral substance of the kidney proper, subcapsular abscesses. Thus the name of kidney carbuncle has been given to such conditions by Israel. These lesions of the kidney are almost invariably multiple, their multiciplicity and size depending primarily on the number of organisms deposited at various time intervals. Such minute abscesses often become confluent. This pathology is in marked distinction to that produced by *B. coli* which, because of low pathogenicity, may pass through the kidney leaving little or no trace of their course except cloudy swelling of the tubules in their convoluted portion, producing an inflammatory reaction in the pelvis proper. Pyelonephritis, and the more advanced condition pyelonephrosis, most commonly caused by *B. coli*, is best considered an ascending infection from the pelvis to the kidney substance proper. This condition shows a different pathologic picture from the conglomerate cortical abscesses above described, although cortical abscesses are common in this condition. The acute diffuse inflammation of the kidney which is caused by blood-borne *B. coli* infection seldom shows abscess formation (Ward [11]). Renal cortical suppurations of staphylococcus origin are dissimilar to lesions caused by *Streptococcus viridans*, for, while localizing primarily in the glomeruli, they cause no pus formation but terminally a chronic glomerulonephritis (Baehr [12]). Larger emboli characteristically cause septic infarcts in the renal cortex, which may break down, forming abscesses similar to those of staphylococcus. *Streptococcus hemolyticus* causes abscesses more commonly than *Streptococcus viridans*, however. Renal tuberculosis, either of the caseocavernous type or that form showing multiple tuberculosis foci in the cortex with or without perinephritis, is of a far more chronic nature.

Of importance in cases of acute unilateral hematogenous suppurative nephritis of the kidney is a diminished resistance of one kidney as a result of previous disease or injury (Israel,[1] Brewer [7] and others). The clinical picture is usually that of mild toxemia, although at times acutely stormy (Brewer,[7] Ward [11]). Localized pain and tenderness in the hypochondrium and costovertebral region are signs of importance. Abnormal urinary findings complete the picture, that is, pus cells,

11. Ward: Surg., Gynec. & Obst. **21**:406, 1915.
12. Baehr: J. Exper. M. **15**:330, 1912.

red blood cells, pus casts and a positive culture from the ureter of the diseased side. Occasionally urinary findings are negative, and Richardson's [5] third conclusion is timely in this respect. "A urine normal on clinical examination does not exclude the possibility of cortical renal abscess." Ordinarily a delayed "appearance time" of phensulphonephthalein from the diseased kidney and a marked diminution in the quantity of the dye eliminated are fairly constant findings. Bart [6] believes the functional test is the best single urinary test.

TYPE CASES OF ACUTE SUPPURATIVE INFLAMMATION OF THE KIDNEY

CASE 1.—J. R. C., a man, aged 57, in December, 1915, began to feel a little below normal, and a "sore" appeared on the left side of the nose, from which considerable pus was discharged. He was confined to bed toward the end of the month because of fever, pain in the limbs and general malaise. Stiffness and tenderness increased in the thigh muscles. He entered the hospital about the middle of February. Physical examination revealed: lungs, clear; heart, normal; spleen slightly enlarged and palpable; tender and palpable left kidney, with pain in the left kidney region radiating toward the back. The temperature was 38 C. (100.4 F.) and the white cell count was 9,800. The Wassermann test was negative. Catheterized urine contained *Staphylococcus aureus*. A specimen from the left ureter contained pus. Cystoscopy revealed diffuse granular cystitis. The results of the intravenous phenolsulphonephthalein test for renal function were: left ureter. appearance time, 8 minutes; fifteen minutes, 4.5 per cent.; thirty minutes, 3 per cent.; total, 7.5 per cent.; right ureter, appearance time, 5 minutes; fifteen minutes, 7 per cent.; thirty minutes, 10 per cent.; total, 17 per cent.

Feb. 18, 1916, the left kidney was removed. Gross Pathology: There were yellowish necrotic areas of pinhead size at the upper pole and a large solitary abscess at the lower pole. On section the pelvis seemed rather small and the wall thick and edematous. Culture from the pus contained *Staphylococcus aureus*.

The patient was discharged well.

CASE 2.—L. S., a man, aged 34, had been in a run-down condition since he had had influenza two years before. He had a slight cough. Two months before entering the hospital, he complained of a boil on his left foot and another on the right jaw. About a month ago, he began to have acute pain in the right lumbar region. Shortly after this he noticed pus in the urine. The pain radiated through to the right midabdomen. The patient complained of sweats, weakness and loss of weight. Physical examination revealed no active tuberculosis. There were signs of thickened pleura or high diaphragm on the right with limitation of motion. The liver and spleen were not palpable. There was marked tenderness over the lumbar region on the right. The temperature was 38.5 C. (101.7 F.). The white blood cells numbered 16,200. Cystoscopy: Cultures from bladder contained *Staphylococcus aureus*. Urine from the left kidney was sterile. According to the history, the right kidney did not function and contained no urine at this time, but a guinea-pig was apparently inoculated with a specimen from the right kidney according to a later note.

August 16: Operation: A perirenal abscess was drained, and nephrectomy was performed. There was pus in the perinephric fat, and there was a cortical abscess at the lower pole of the right kidney.

Gross Pathology: At the lower anterior pole there was a slightly projecting capsular abscess about 2 cm. in diameter. On section, proceeding from

the abscess toward the pelvis, multiple small focal abscesses were seen. The remainder of the kidney appeared to be quite normal. The pelvis was not dilated or thickened. Culture from pus contained *Staphylococcus aureus.*

The patient was discharged well.

DISCUSSION

There is little to be said regarding these fairly typical cases except to point out a preceding skin infection of a staphylococcus nature, and later isolation of cocci of the aureus group from the metastatic lesions. In Case 2 the perinephric fat was involved in contradistinction to Case 1. Such a combined renal-perirenal suppuration must always be borne in mind when simple drainage of the abscessed fatty tissue fails to clear the symptoms.

PERINEPHRIC ABSCESS

These abscesses are located in the perirenal fat, and in a pure state they are wholly outside the kidney. Under the caption "primary perinephric abscess" I exclude all perinephritic collections of pus spread by continuity from adjacent diseased sources, except the kidney cortex. This classification excludes perinephritis accompanying pyonephrosis, nephrolithiasis and renal tuberculosis. In the majority of primary cases there is an extension of a minute cortical abscess, probably seldom the reverse. It is stated, however, that a pure perirenal abscess may be the only internal lesion from some cutaneous infection. Such cases may show no abnormal urinary findings and clear readily by simple drainage of the part in many instances.

The picture caused by these extranephric collections of pus is more severe than that caused by a suppurative kidney proper. The toxemia may be more marked, probably because of rapid extension of involvement in the loose tissue. Depending on the location of pus—proximity of the upper or lower pole—the signs are often referred to the base of the lung and pleural cavity, or the upper right or left quadrants and paravertebral region of the costovertebral junction. A history of boils, symptoms of toxemia, marked tenderness over the costovertebral angle and high diaphragm on the affected side are for the most part constant. Roentgenograms are a decided diagnostic advantage in most cases.

TYPE CASES OF PERINEPHRIC ABSCESS

Case 3.—P. G., a woman, aged 24, gave a history of having had several boils on the buttocks about a month before. On May 1, 1920, she had had a mild chill and fever. The following day she had had a dull pain in the right shoulder. The appendix was removed the next day by the patient's physician, who noted no inflammation of that organ. The patient did well for a few days, and then her former symptoms returned. A large collection of pus was drained in the right flank extraperitoneally. For about two weeks she was free from pain, but she complained of chills and fever and lost 30 pounds (13.6 kg.) in weight. The abdomen was opened a second time, and nothing was found.

The patient entered the University of California Hospital three months after her primary trouble. Physical examination revealed: a blowing systolic murmur over the base of the heart; extreme rigidity and tenderness in the right hypochondrium and lumbar muscles; slight swelling, mottling and congestion over the lumbar region. The liver and spleen were not enlarged. The Wassermann test was negative. A blood culture was negative. The urine was normal. White blood cells numbered 26,600. There were 93 per cent. of polymorphonuclear cells. The roentgen ray showed: obliteration of the kidney and a psoas outline on the right. Operation revealed an abscess around the lower pole of the right kidney. The kidney was removed, but no gross pathologic condition was found. Cultures from the pus contained *Staphylococcus aureus.*

Case 4.—W. H. K., a man, aged 43, entered the hospital on Feb. 13, 1916. Five months before he had had an infection of the right hand, with a hard core. This condition cleared up, and he then began to be troubled with pain on the anterior surface of the left thigh. The pain migrated to the ankle joint, which became swollen, but the swelling subsided in a week. While being treated for the condition in the leg, he noted a dull aching pain starting low down in the right side of the abdomen and radiating up to the kidney region. This pain localized in the right upper quadrant and the right lumbar region was "sore." The patient felt weak, his appetite was poor and he had lost weight. He had no chills or sweats.

Examination revealed a sick looking, anemic man, with eyes sunken and yellowish sclerae. The heart was normal. Dulness at the right base seemed to be due more to a high diaphragm than to a pleural collection. Breath sounds still were heard over this area. There was no friction sound. It was impossible to palpate the upper right side of the abdomen on account of rigid abdominal muscles. There was decided tenderness over the right costovertebral angle. The temperature was 100.4 F. (38 C.). White blood count, 20,000. Catheterized urine from the right kidney did not contain pus; the culture was negative. The phenolsulphonephthalein "appearance time" was 6 minutes (intravenous); in fifteen minutes it was 23 per cent.; in the following fifteen minutes, 11 per cent. The roentgenogram showed an area of rarefaction in the shaft of the femur 2 inches (5.08 cm.) below the trochanter with periosteal reaction over it. The condition was diagnosed as osteomyelitis. Screen examination of the chest showed a high and somewhat flattened right diaphragm. Operation: Pus was drained from the superior and posterior parts of the fatty capsule of the right kidney. The kidney seemed intact and was not removed. Culture from the pus was *Staphylococcus aureus.*

Case 5.—A. S., a man, aged 49, entered the hospital with a carbuncle on the neck of three weeks' duration. His present illness started a week ago with pain in the left side of the chest on coughing and deep inspiration. He complained of loss of appetite, weakness and night sweats. Physical examination revealed a normal heart, diminished scarcely audible breath sounds over the left base, with corresponding dulness and diminished vocal fremitus, and no râles. Respirations were short, and attempted deep breathing caused pain low in the left side. The left lumbar region was more prominent than the right, extremely tender and slightly edematous. The temperature was 102 F. White blood count, 29,000. The urine was normal. The chest was tapped, but was dry. Operation: two hundred and fifty cubic centimeters of pus were removed from the perirenal region; the kidney was not removed. Pus culture contained *Staphylococcus aureus.* There was a marked drop in temperature following operation, and the patient was discharged in three weeks, well.

Case 6.—L. J., a man, aged 24, three months before began having a series of boils. These extended over a period of two months. The last boil was on the right forearm and was quite severe. During this interval of time, the patient was treated for an abscess in the palm. About a month later

he complained of an acute pain in the left axilla, felt weak and ran a temperature of 102 F. He entered the hospital after a few days, complaining of pain in the left axilla; his afternoon temperature was high and he was weak. Physical examination revealed: a normal heart. The left base showed signs of fluid up to the angle of the scapula; dulness to flatness with diminished to absent breath sounds and Grocco's sign on the right were present. Liver and spleen were not palpable. The back was blistered (medication) over the left upper lumbar region. There was tenderness over the costovertebral angle. White blood cells numbered 18,600. The urine was clear; white blood cells, double plus. Blood cultures were negative. Thoracentesis was performed: fluid was found; white blood cells, triple plus; culture negative. A second tap yielded fluid of the exudative type; white blood cells triple plus, culture negative. There were 21,800 white blood cells. The roentgen ray revealed: obscure left kidney shadow, fluid at the left base; normal spine. Operation: Pockets of pus were found extending upward to the upper pole of the left kidney. Cultures from the pus contained *Staphylococcus aureus*. The roentgenogram showed no signs of fluid at the left base on discharge.

The patient was discharged well.

Case 7.—A young man entered the U. S. Naval Hospital, Mare Island, Calif., 1919, complaining of chills, fever, sweats and pain in the right upper lumbar region. There was a history of boils, the last one clearing two weeks previously. Dulness was noted at the right base, with diminished fremitus and breath sounds. The medical officer in charge of the ward aspirated thick pus by plunging the needle through the ninth interspace. Pus cultures contained *Staphylococcus aureus*. The diagnosis was empyema. The pleural cavity was opened low down in the postaxillary line. No pus was found. The needle was inserted through the lateral curve of the diapragm in the direction of the kidney, and pus was located. It was drained extrapleurally through the diaphragm and chest wall. Cultures from the pus contained *Staphylococcus aureus*.

DISCUSSION

All of these cases give a history of a staphylococcus skin infection followed in a comparatively short interval of time by pus formation around the kidney region from which was isolated the same organism. In view of opinions expressed above regarding the origin of this condition, it is important to recognize the fact that all of these patients made uncomplicated recoveries by simple drainage, with but one exception. In this patient, Case 3, the kidney, after nephrectomy, appeared normal. Unfortunately, no microscopic study was made. This case is in marked contrast to Case 2 of the suppurative kidney group, which showed, in addition to free pus around the kidney, abscesses in the renal cortex.

The striking clinical features in this group are the basal chest signs caused by these infradiaphragmatic collections of pus. The observation is old and recognized. The sterile irritative exudate found in Case 4 suggested contiguous pus formation, principally because of many pus cells without demonstration of the causative organism.

MUSCLE ABSCESSES, SUPPURATIVE JOINTS, ETC.

In suppuration of the muscles, staphylococci play their rôle, not by local extension from a skin lesion, but by metastases into more distant muscle groups by way of the blood stream. Subcutaneous

abscesess are not unusual after boils, but in many instances they are caused by continuity. The subcutaneous abscesses caused by streptococci are commonly metastatic. They come occasionally after peritonsillar abscess. Acute pyogenic myositis is commonly seen in the iliopsoas. Given a primary focus, however, any muscle or muscle group may become the seat of pyogenic inflammation, either spontaneously or predisposed by trauma. Acute polymyositis is possibly of *Staphylococcus aureus* nature (Schmitz [5]). Trauma, as in the long bones, predisposes muscles (possibly joints and kidneys) to staphylococcus infection.

Commonly patients complain of pain in the joints, either single or multiple, in the course of intermittent blood stream infection—toxic synovitis. Staphylococcus septicemias may give rise to single or multiple pyemic joints from which cocci are readily grown. Finally, an abscessed joint may be the only manifestation of a focal skin infection. Regarding joint conditions in general, the streptococcus plays a far more important part.

Rarely an abscess in the periprostatic tissue may be a metastatic manifestation of a carbuncle (Kretschmer [13]).

TYPE CASES OF MUSCLE ABSCESS

Case 8.—A man, about 30 years of age, entered the U. S. Naval Hospital at Mare Island, Calif., in 1919, with a high fever and a ligneous inflammation of the back of the neck. Three weeks previously the patient had suffered from acute rhinitis, followed by a series of "pimples" just inside the nares. About a week later he began to have slight difficulty in swallowing and three days previous to entrance his neck became painful, hard and indurated. The patient presented the picture of a toxic person unable to move his head on account of pain and stiffness. The back of the neck was of wooden consistency, swollen, hot and painful. There was no redness of the throat or bulging of the postpharyngeal wall. A slight localized discoloration in the region of the left anterolateral thigh muscles was noted. Inquiry revealed that while he was being lifted from the ambulance, he hurt his thigh on the end of a litter which was lying folded adjacent to him. The following day a small amount of pus was located by aspiration deep in the muscles of the neck. The neck was opened the next day and pus was found deep in the dorsal muscles. Culture contained *Staphylococcus aureus.* Three days later pus was aspirated from an abscess deep in the lateral rectus muscle, subjacent to the traumatized area. Culture revealed *Staphylococcus aureus.*

Case 9.—A child, aged 5, was just convalescing from a mild case of chickenpox. The vesicle distribution was sparse, and the crusted lesions were clearing. In the second week of the disease, the child began to complain of pain over the paravertebral region (erector spinae group). Simultaneously the temperature became elevated, and there was extreme tenderness over the muscles of the back at about the level of the first lumbar vertebra on the right. Tumefaction was slight over this area, and local heat was almost imperceptible. A needle puncture revealed pus deep in the erector spinae group. The abscess was incised. Culture revealed: *Staphylococcus aureus.* There was no evidence of a pox lesion in the close proximity of the abscess.

13. Kretschmer: Surg., Gynec. & Obst. **32**:259, 1921.

CASE 10.—G. T., a man, aged 37, about a year ago suffered from a carbuncle on the back of his neck, which lasted about a month. Shortly after healing, the patient complained of a painful swelling on the back, which was opened and pus removed. While the abscess was still draining, the patient noted a swollen, painful left thigh, which was incised and much pus removed. About this time, the left upper arm began to swell, and he was very ill with fever, pain and sweats. No surgical treatment of the bone was instigated, but pus was removed on four different occasions from the soft parts of the arm, which persisted to drain. Osteomyelitis was discovered some time later by roentgen ray, and it is reasonable to suppose that the entire disturbance of the soft tissues of the arm was contiguous to a missed osteomyelitis. The patient was operated on immediately after his admission to the hospital, and extensive sequestration of the humerus was found. The pus showed *Staphylococcus aureus* on culture.

DISCUSSION

In these cases it is logical to assume a metastatic abscess from the primary skin condition. Case 8 shows well the localization at the site of trauma. In Case 9 we assume a secondarily infected varicella lesion as the primary focus, with the subsequent dispersion of staphylococci to more distant parts. Such a condition is rare following chickenpox. We are forced to assume in Case 10 a relation between the carbuncle and the multiple abscesses, for these lesions were well healed when the patient was examined, and no cultures or culture reports were available. The relationship between the carbuncle, abscesses and osteomyelitis is a well established clinical condition caused by a common organism. With the isolation of *Staphylococcus* aureus from the pus of the humerus we are probably safe in our assumption of the cause of the other conditions. Whether these abscesses were in the muscle proper or the subdermal fatty tissue is difficult to know.

ACUTE PYOGENIC OSTEOMYELITIS

Primary osteomyelitis does not exist as such except in a compound fracture. In the majority of cases, acute osteomyelitis is a blood-borne staphylococcus infection. (See experimental work of Rodet,[2] Lexer [3] and others.) As in the other conditions under discussion, the blood stream infection is transient in the majority of cases. However small the primary lesion, probably the majority are of a focal skin condition which offers a portal of entry for the causative coccus.

As is well known, traumatism commonly lowers the resistance of a particular bone so that the organisms more readily produce their destructive effect. It is possible that an injury may be the determining factor in localizing the site of invasion. The characteristic lesion is a panosteitis, a progressive involvement of cancellous bone, periosteum, cortex and marrow cavity in the order named. The long bones are affected far more commonly, the causative organism localizing in one

or the other extremity in the cancellous substance. Ochsner and Crile [14] believe that the organisms localize at the place where the blood flow is most sluggish; for example, on the diaphyseal side of the epiphyseal line. According to Starr,[15] the infective agent lodges in the juxta-epiphyseal region of a long bone, passes along the line of the epiphysis to reach the periosteum, stripping this structure from the cortex and thence passes via the haversian canals to the medullary cavity. The marrow is thus involved secondarily to the periosteal infection rather than by extension through the cancellous tissue, from which it is involved less frequently. At a more advanced stage, large portions of the cortex become necrotic and, isolated from the living bone, lie in the pus-bathed medullary cavity as sequestra.

Acute osteomyelitis is most disastrous in its sequelae if allowed to run an uninterrupted course. Relief from such an acute condition is truly an emergency surgical procedure. Surgeons who wait for roentgen-ray confirmation prolong the disease by months or years.

It is not within the scope of this paper to comment on different surgical methods. The typical case runs so true to form that there should be little diversity of opinion regarding the diagnosis. The history of furunculosis or an infected skin abrasion, especially if preceded by bone trauma, is of prime importance. Nasopharyngeal infections are less important (Bloomfield,[16] on normal flora of nasal passages). The clinical picture of toxemia accompanied by sudden severe pain in the neighborhood of a joint, with a point of local tenderness over the region of the metaphysis, are first indications of the clinical picture. If allowed to continue, the characteristic tume-faction of the part develops. The adjacent joint is seldom involved primarily. A neighborhood serous synovitis may occur, but direct extension through the epiphysis is a late complication.

ACUTE OSTEOMYELITIS

CASE 11.—J. N., a boy, aged 13, first entered the hospital in July, 1916. The child was toxic on admission, with high fever and signs of septicemia. He was studied closely, and during the first two weeks many organs became involved, the principal of which were the pericardium, lungs, joints, pleura and left femur. Staphylococci were repeatedly grown from the blood. An operation for osteomyelitis was unfortunately delayed for two weeks, and as a consequence the boy went through months of surgical treatment for relief of the suppurating femur. He returned to the outpatient department two years after the onset of the primary trouble, with a complaint of pain about the right knee; there was no swelling or redness. He entered the hospital after four days' delay, where a diagnosis of osteomyelitis of the right tibia was made.

14. Ochsner and Crile: Surg., Gynec. & Obst. **31**:263, 1920.
15. Starr, C. S.: Acute Hematogenous Osteomyelitis, Arch. Surg. **4**:567 (May) 1922.
16. Bloomfield: Bull. Johns Hopkins Hosp. **32**:290, 1921.

The blood culture was again positive for *Staphylococcus aureus*. Operation: Pus was removed from the periosteum and medullary cavity. The cultures contained *Staphylococcus aureus*.

CASE 12.—F. B., a boy, aged 12, was first seen at the Protestant orphanage on May 24, 1920, with a complaint of a sore on the right leg and a painful tender knee. He did not enter the hospital until May 29, a dangerous delay. On entrance there was noted a small purulent ulcer over the right tendo-achilles at the height of the shoe top. The right leg was swollen from the knee joint to the middle of the thigh, slightly reddened and tender. The knee joint had a small excess of fluid. The boy complained of much pain in the swollen leg. The heart was normal, temperature 39 C. (102.2 F.) *Staphylococcus aureus* was isolated from the blood and ulcer on the ankle. Operation: Subperiosteal pus was evacuated. Two days after operation the blood culture was negative, but the temperature remained elevated. Operation: The lateral half on the lower third of the shaft of the femur was cut away, and a purulent medullary cavity was exposed. Cultures contained *Staphylococcus aureus*. The boy remained in the hospital for a year and four months. During the interval several operations were performed for the removal of sequestra. When he was discharged his leg was still draining from a sinus 10 cm. above the lateral condyle.

CASE 13.—F. B., a boy, on Nov. 15, 1922, jumped from an elevation of 2½ feet (76.2 cm.) to the ground. He did not fall; he walked home, but had pain and complained of soreness in his left leg. He returned to school the next day, but the leg was painful. He started to school the following day, but was forced to return because of swelling and great pain in the leg. He was confined to bed for two weeks before coming to the hospital. On further questioning a small scar was found on the right wrist, which the patient stated was a "sore." It was discharging, and it healed about a month before the present trouble started. On admission, the boy was markedly toxic, with a temperature of 39 C. (102.2 F.) and a white count of 22,000. The left lower leg was swollen from the knee to the foot, with a reddish discoloration over the middle third, especially on the medial side. Edema was marked, and pressure along the crest caused considerable pain. Operation was immediately performed. Four hundred cubic centimeters of purulent material were removed. The periosteum had been completely separated from the bone, and the marrow cavity was purulent for a distance of 10 cm. Cultures contained *Staphylococcus aureus*. The boy's leg was still draining when he was sent to another hospital fourteen days after operation. Additional surgical procedure will be necessary.

The history was obtained from the patient's mother and uncle who have a very limited knowledge of English.

DISCUSSION

The eleventh case is of interest because the boy was first seen when suffering from a general septicemia, the acute osteomyelitis of the left thigh being one of the many manifestations of the generalized pyemia. The blood stream infection was proved by repeated positive cultures of *Staphylococcus aureus*. The operation on the thigh was not performed early, and therefore much sequestration resulted. He has had repeated operations since. It is interesting to note that two years after the first operation he again was seen with symptoms of acute osteomyelitis of the opposite tibia, and the blood culture taken the day before the operation was again positive for *Staphylococcus aureus*. Many cases of recurrent osteomyelitis of different long bones are reported, the

focus being the site of the original or subsequent bone infections. It has been suggested that such cases represent relative specificity of the particular strain of staphylococcus to bone lesions. This is difficult to affirm, knowing the characteristic rôle played by staphylococcus in regard to acute osteomyelitis.

The twelfth case represents a typical case of osteomyelitis, the site of focal entrance being an abrasion of the skin caused by rubbing of the shoe. Cultures from the ulcer, blood and marrow pus all contained *Staphylococcus aureus*.

The thirteenth case presents the typical history of trauma followed by symptoms of osteomyelitis and proved by operation to be of a staphylococcus nature. One need go back into the boy's history only a month to find that he suffered from a boil on the right arm, the scar of which is still obvious. This naturally brings up the question of whether or not cocci enter the cancellous bone and remain quiescent until lit up by trauma.

CONCLUSION

However apparently harmless skin infections appear to be, the more serious complications should always be borne in mind. To many physicians, boils in adult patients rarely bring to mind other than the examination of the urine for sugar. So characteristic are the metastatic complications of staphylococcus focal infection, particularly boils and carbuncles, that their recent occurrence should guide one in the diagnosis of certain more serious internal suppurative conditions.

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A CONTRIBUTION TO THE BIOCHEMISTRY AND TREATMENT OF CHRONIC NEPHROSIS (EPSTEIN)*

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Following many observations made—clinical and chemical—in various forms of renal disorders, Epstein,[1] in 1917, reported what he regarded as a clinical and pathologic entity, called by him a chronic nephrosis, which clinically simulates, although in many respects it differs from, the commonly known forms of chronic parenchymatous nephritis. Briefly, this condition is regarded as one of a metabolic nature, in which the renal and other clinical manifestations are concomitant or secondary in point of development and importance. Both the clinical and laboratory findings are characteristic in the pure form of the disease. Its origin is slow, insidious and of unknown etiology. The first intimation the patient may have of the disease is the pallor and evidence of edema. The course is protracted. Objectively, there is a general anasarca, oliguria and absence of increase in the blood pressure and cardiac hypertrophy. It occurs, as a rule, in relatively young people. The urine shows a high specific gravity, a marked albuminuria with or without casts, and the absence of blood elements. The blood serum has a milky appearance; its total protein content is low; the albumin-globulin ratio is reversed, and the globulin may be both relatively and absolutely increased. The blood shows a high cholesterol content.

The treatment recommended—a high protein diet—is based on the theoretical conception of the cause of the edema. The latter is attributed to a disturbance between the intracapillary pressure and osmotic force of the blood. This idea is based on the observation of Starling, on the osmotic effect of the blood proteins. The marked loss of protein, or colloid content of the blood, characteristic of the disease, lowers the osmotic pressure of the blood, and on account of this the osmotic force of the tissue fluids becomes relatively increased. This leads to the attraction of fluid to the tissues, with the production of edema.

The diet is essentially of a high protein, low carbohydrate, low fat nature. By this means it is hoped that the high protein content will replace the protein lost in the urine, and the low fat and low carbohydrate may influence the body to utilize all the protein ingested and the excess lipoids already present in the blood.

That this disease is a metabolic disturbance is suggested by the lipoidemia, and in some cases by the presence of a hypothyroid state

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1. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, Am. J. Med. Sc. **154**:638, 1917.

with a decreased basal metabolic rate. This is further suggested by the good results obtained at times, following the administration of thyroid extract.

The foregoing description typifies the pure form of the disease, but since renal disorders are by no means always of a pure type and do not show a clear cut course, Epstein points out, this nephrosis may be associated with, or occur late in, the course of a chronic nephritis. From the therapeutic point of view, it is important to recognize this possibility. With the subsiding of the nephritis, treatment should be directed toward the nephrosis.

Since the publication of Epstein's original article and his subsequent articles [2] on this subject, little has appeared in the literature. Both favorable and unfavorable clinical results of the effects of feeding a high protein diet are recorded by a few observers, and there are still fewer records of detailed observations. The data of the few reports are practically all clinical, with but little accompanying findings of the blood chemistry. Of special interest are those of Kahn,[3] who records the essential analyses of the blood serum in a series of cases studied both before and after feeding high protein diets. Based on these observations, and those of Kerr, Hurwitz and Whipple on the stability of the blood serum protein level, of Böhm and Reiss on the concentration of serum protein made with the refractometer, and of Rowe on the effects of high protein diets on the albumin-globulin fractions, Kahn concludes that chronic nephrosis, described by Epstein, is of rare occurrence. He states that among all of his series not one case of this "metabolic" type was found; that on feeding patients suffering from "chronic parenchymatous nephritis" a high protein diet, the albumin-globulin ratio was not affected, and the edema did not diminish to the slightest extent. He further concludes that feeding such patients on such a high protein diet is a "risky undertaking." This criticism is rather severe if he refers to chronic nephrosis. The data of the four cases Kahn records, which were studied both before and after feeding, partly bear out his views. An analysis of the data, however, shows that in none of these cases do the chemical findings correspond to the Epstein type of chronic nephrosis. Table 1 shows the values Kahn found in these cases. Since no case of this "metabolic" type was found, it is apparent that the results obtained are not surprising.

Numerous observations made in this hospital corroborate one view held by Kahn, namely, the uncommon occurrence of chronic nephrosis. The case recorded here is the first noted during a routine examination of all cases of a renal nature admitted during the last three years.

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2. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. Med. Sc. **163**:167, 1922.

3. Kahn, Max: The Protein and Lipin Content of Blood Serum in the Nephritides, Arch. Int. Med. **25**:112, 1920.

Our case does not represent the pure form described by Epstein, but corresponds to a nephrosis, probably superimposed on, or associated with, a chronic nephritis. Epstein points out that such cases as this mixed type are not uncommon in his experience. The presence of a nephrosis in our case is demonstrated by the chemical analyses of the blood (high cholesterol and low protein content, and reversal of albumin-globulin ratio), the clinical history of the onset and course of the case following the treatment with a high protein diet. The object here is to present briefly the clinical history and laboratory data obtained throughout a period of six months.

TABLE 1.—*Effect of Feeding a Protein Rich Diet in Cases of Parenchymatous Nephritis*

Case	Period	Total Protein	Albumin	Globulin	Globulin, Percentage
4	Before	4.24	2.93	1.31	31
	After	5.27	3.59	1.68	32
8	Before	7.60	4.26	3.34	44
	After	7.75	4.50	3.25	42
9	Before	5.76	3.75	2.01	35
	After	6.12	3.92	2.20	36
11	Before	6.09	4.14	1.95	32
	After	6.37	4.46	1.91	30

REPORT OF A CASE

History.—A woman, aged 37 years, was first admitted on Oct. 23, 1922, to the medical wards of the Montreal General Hospital, in the service of Dr. F. G. Finley. She was apparently in good health until on Oct. 1, 1922, when she first noted swelling of both feet. There were no other complaints. The family and personal history were irrelevant.

Physical Examination.—The patient appeared comfortable in any posture. There was marked pallor. The ocular and buccal mucosae were pale. The legs were edematous. The blood pressure was: systolic, 210 mm. of mercury; diastolic, 116 mm. of mercury R. C. D. $\frac{111}{3/10 \text{ cm.}}$ (R. C. D. refers to the areas of relative cardiac dulness found on percussion). A systolic murmur at the apex replaced the whole of the first sound. The electrocardiogram was normal. Breath sounds were vesicular. Many loud sibilant rhonci were heard all over the chest. In the fundi there was degeneration of the arteries but no exudate or hemorrhage. The patient had marked albuminuria and there were many casts. The specific gravity was 1.030.

The renal test meal showed a tendency toward fixation in density and volume in the periodic specimen, and a nocturnal polyuria. The blood urea nitrogen was 24 mg. per 100 c.c. creatinin 1.5 mg. The urea concentration of the urine following ingestion of 15 gm. of urea was 1.29 per cent. after the first hour and 2.04 per cent. after the second hour. There were 3,200,000 red blood cells, 7,800 white blood cells and 50 per cent. hemoglobin. The usual treatment, including a salt free, low protein and restricted fluid diet, and purgation, was given. Throughout the course in the hospital, the temperature was normal. On Nov. 1, 1922, the patient was discharged slightly improved. There was still some edema present about the ankles. The blood pressure was: systolic, 180, diastolic, 100.

Second Admission.—The patient was readmitted on Feb. 3, 1923, with a history of being well only three days after discharge from the hospital. On admission the positive findings were: marked pallor, general anasarca, oliguria and good appetite. The blood pressure was: systolic, 214, diastolic, 140

R.C.D. and heart sounds were the same as during the former admission. The complete analyses of blood, urine, etc., are recorded in Tables 2, 3 and 4. The treatment and laboratory analyses will be discussed below. The patient's weight on admission was 171¾ pounds (77.9 kg.), and on discharge, 123 pounds (55.7 kg.). The blood pressure on discharge was: systolic, 138, diastolic, 76. On April 19, 1923, the patient was discharged in a much improved condition. There was no edema present.

COMMENT

The tables give the complete laboratory data obtained. Tests made during the early period in the hospital showed a marked impairment in the renal function. The renal test meal showed a marked salt, water and nitrogen retention; a fixation both in the density and volume in the periodic specimens, and a diminished concentration of the nitrogen of the night urine. The excretion of total solids, and the day-night solids ratio also showed impairment. This is also shown by the increase in the concentration of urea nitrogen in the blood and a diminished concentration of urine urea following the ingestion of 15 gm. of urea. The analysis of the blood serum proteins, Table 2, showed a much diminished concentration of total protein and a reversed albumin-globulin ratio. The cholesterol content of the blood, Table 2, was greatly increased. Correlating the foregoing data with the clinical history of the onset and the physical examination, the picture is that of chronic nephritis, associated with chronic "nephrosis."

During this period of observation the patient was on a salt free, low protein and restricted fluid diet, with the exception of the day on which the renal test meal was given. On this diet there was a general clinical improvement, as occurred during the former period in the hospital—a diminution in the amount of edema and a fall in the blood pressure to: systolic, 120; diastolic, 70. The weight dropped to 123 pounds, but the total protein content of the blood serum and the albumin-globulin ration were little altered, and there was still edema of the legs and ankles.

Based on these observations—the persistence of edema—the unchanged chemical state of the blood and the unsuccessful treatment of the patient during the first admission to the hospital—a high protein diet approximating that described by Epstein was commenced. The data shows the progress made. The results of the renal test meal on admission and prior to discharge are of interest. The latter shows a marked improvement in function. There is a normal water balance, only a slight salt retention and a normal nitrogen balance. The variation in volume and density of the periodic specimen is normal. The excretion of total solids is increased, above that found on admission, on a diet of the same total solid content. Improvement is also shown by the fall in the cholesterol content of the blood to near the normal level (normal 140 to 180), and by the increased concentration of urine urea following the ingestion of urea. That some impairment is still

TABLE 2.—*Blood Serum Protein Estimations*

Date	Total Protein	Albumin	Globulin	Globulin Percentage	Cholesterol Gm. per Cent.
February 11	3.9	1.30	2.60	66.6	0.781
February 27	3.7	1.45	2.25	61.0	.....
March 18	5.8	2.88	2.98	51.3	0.426
April 17	7.72	4.67	3.05	39.6	0.301

TABLE 3.—*Kidney Function*

Date	Blood			Urine; Urea Concentration, Percentage	
	Urea Nitrogen, Milligrams per 100 C.c.	Creatinin, Milligrams per 100 C.c.	Sodium Chlorid Percentage	First Hour	Second Hour
February 3	52	1.46	0.6682	....	....
8	22	1.50	.....	....	....
12	20	1.50	.....	0.96	1.00
21	28	1.58	.....	0.78	0.84
March 7	52	2.0	.....	....	....
9	..	....	0.6188	....	....
15	56	1.53	0.6188	....	....
19	48	....	.....	....	....
21	54	1.62	.....	....	....
April 9	50	....	0.5445	....	....
18	55	1.42	0.6109	1.41	2.00

TABLE 4.—*Salt, Nitrogen and Water Balance*

Date	Intake			Output		
	Water	Sodium Chlorid	Nitrogen	Water	Sodium Chlorid	Nitrogen
March 8	1,750	6.0	15.6	550	11.6	9.0
9	1,750	6.0	15.6	950	9.2	8.9
10	1,750	6.0	15.6	1,020	13.9	6.3
11	1,750	6.0	15.6	870	12.6	9.2
12	1,750	6.0	15.6	950	14.0	11.1
13	1,750	6.0	15.6	1,250	5.5	13.2
14	1,750	6.0	15.6	1,000	6.0	16.8
15	1,750	6.0	10.2	1,350	5.4	9.8
16	1,750	6.0	15.6	1,475	7.0	10.0
17	1,750	6.0	15.6	1,400	5.9	11.0
18	1,750	6.0	15.6	1,380	7.1	14.5
19	1,750	6.0	15.6	1,770	4.9	14.6
20	1,750	6.0	15.6	1,320	5.8	16.6
21	1,750	6.0	15.6	1,350	5.9	14.8
22	1,750	6.0	15.6	1,125	6.2	9.5
23	1,750	6.0	15.6	1,260	5.0	15.1
24	1,750	6.0	15.6	1,120	4.0	12.9
25	1,200	6.0	15.6	900	5.0	12.3
26	1,750	6.0	15.6	1,230	5.9	8.5
27	1,750	6.0	15.6	1,260	7.2	14.3
28	1,750	6.0	15.6	1,400	5.0	15.6
29	1,750	6.0	15.6	1,000	3.6	16.7
30	1,750	6.0	15.6	1,350	5.4	10.3
31	1,750	6.0	15.6	1,400	6.1	13.7
April 1	1,200	6.0	15.6	980	5.8	12.54
2	1,750	6.0	15.6	1,500	7.8	12.1
3	1,750	6.0	13.8	1,370	6.5	14.6
4	1,250	6.0	15.6	1,370	6.0	14.3
5	1,750	6.0	15.6	1,240	6.9	15.1
6	1,750	6.0	15.6	1,000	5.7	12.6
7	1,750	6.0	15.6	1,125	7.2	16.1
8	1,750	6.0	15.6	1,100	4.4	15.8
9	1,600	6.0	15.6	1,255	6.2	17.8
10	1,200	6.0	11.9	1,325	6.3	10.1
11	1,750	6.0	15.6	1,070	4.7	14.0
12	1,750	6.0	15.6	1,260	6.0	16.0
13	1,750	6.0	15.6	1,100	7.4	13.3
14	1,750	6.0	15.6	1,250	7.0	12.4
15	1,750	Renal meal day				
16	1,750	6.0	15.6	1,125	7.2	13.3

present, is shown by the persistence in the increased amount of blood urea nitrogen, a nocturnal polyuria in the renal meal, and diminished day-night ratio of excretion of solids. Accurate data of the effect of the diet on the salt, water and nitrogen balance were not recorded early in the period of observation. To obtain data on this phase of the subject, the patient was placed under routine metabolism orders. All food and fluids were prepared in and served from the metabolism diet kitchen. The collection of urine was accurately controlled. The total salt, water and nitrogen content of the diet, including the salt and water content of the solid food, were calculated from the Atwater-Bryant food tables. A few residues were calculated and subtracted on the same basis. A constant diet was given, and it will be noted in Table 9 that the patient had, as she stated, a good appetite, little residue being recorded in only a few instances during the entire period of observation. It will be noted also that although sufficient salt was given daily to make the food palatable, this did not affect the favorable progress of the case and the end result. The salt was not only totally eliminated, but during the entire period in which records were kept, forty days (from March 8 to April 16) there was a total excretion of 47 gm. of salt (calculated as sodium chlorid) in excess of that ingested. This is contrary to expectation, if this is a case in which the only lesion present is that in which the kidneys are unable to excrete salt. This loss of salt may partly explain the clinical result. The patient was discharged on April 19, 1923, weighing 123 pounds; the edema had completely disappeared. Since the weight remained the same after the institution of the high protein diet in spite of the complete absence of edema, it appears reasonable to assume that the patient actually gained real tissue weight on this diet. This corresponds with the improved clinical appearance of the patient. The various tables show that with the clinical improvement there was practically a return to normal in the protein composition of the blood serum, including the total amount and albumin-globulin ratio. The data also show that the high protein diet did not at any time react unfavorably.

SUMMARY

A case of chronic nephritis associated with a chronic nephrosis is recorded. The usual treatment of chronic nephritis, including restriction of salt water and nitrogen, caused improvement to a certain stage, which became stabilized; the edema still persisted. Following the institution of a high protein diet there was no evidence of a further increase in the nonprotein nitrogenous elements in the blood and no clinical symptoms suggestive of any harmful effects. The end result was a marked improvement in the clinical picture, with a complete disappearance of the edema. Improvement was also shown by the chemical state of the blood and renal function tests.

A STUDY OF THE BLOOD OXYGEN IN DIABETES MELLITUS *

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A patient with diabetes mellitus, in the wards of the Peter Bent Brigham Hospital, was observed to have a slight but definite cyanosis, for which no explanation could be found. A sample of venous blood from the arm revealed on analysis a marked increase in the oxygen unsaturation. The venous oxygen unsaturation of several other diabetic patients was found to be similarly though not so markedly increased, and it seemed worth while to study a small group of these patients in this respect.

Accordingly, samples of anticubital venous blood were taken without stasis and under oil from thirty-four unselected diabetic patients, while the patients were at rest in bed, and the samples were analyzed by the method of Van Slyke and Stadie [1] for oxygen content and oxygen capacity, the oxygen unsaturation being calculated by subtracting the oxygen content from the oxygen capacity. Duplicate analyses were made in each case. It was found that thirty of the patients had an oxygen unsaturation which was greater than the average normal found by Lundsgaard [2] and greater than the average of twelve control subjects. The average venous oxygen unsaturation of all the diabetic patients was 8.98 per cent. by volume, as compared with 5.64 per cent. by volume in the control series, an increase of 59 per cent. (Chart 1). Three of the four patients with a venous oxygen unsaturation lower than the average normal had quite low basal metabolic rates, and the other one had active pulmonary tuberculosis. A low basal metabolism might decrease the oxygen unsaturation because of the low total oxygen consumption of all the tissues and there would be a consequent decrease in the amount of oxygen extracted from the hemoglobin by the tissues. Active tuberculosis, with its accompanying rapid heart rate, should tend to have a low oxygen unsaturation because of the increase in the rate of blood flow.

Only two of the patients had cyanosis, and in both of these it was of slight degree. Several others had a somewhat dusky color, but the remainder were essentially normal in color. Cyanosis might have been expected in more of the patients with the higher venous oxygen unsaturations, except for the fact that the arterial blood was practically

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1921.
2. Lundsgaard, C.: J. Biol. Chem. **33**:119, 1918.

saturated with oxygen, bringing the average oxygen unsaturation of the capillary blood in the majority of cases below the threshold for cyanosis (Lundsgaard [3]).

Fourteen of the patients had the analyses of the venous blood made two or more times during the course of treatment. Of these fourteen patients, all but four showed a definite shift of the oxygen unsaturation toward normal as the treatment progressed (Fig. 2). However, many of the other patients did not have their first and only analysis made until they had been under treatment for a considerable length of time, and still showed very high figures for oxygen unsaturation, so that it cannot be definitely concluded that treatment reduces the increased unsaturation. One patient (No. 20) had the first analysis made when she was suffering with a sinusitis and had slight fever, with an accompanying rapid heart rate and increased metabolism. Another (No. 21) had marked acidosis with an elevated basal metabolism at the time of the first determination. In both cases the figures were normal at first, but higher ones later when the diabetes was uncomplicated. The two first determinations were not charted. Patient No. 21 subsequently had an approximately normal oxygen unsaturation again, as he improved under treatment.

Patients 18, 19, 22, 23, 24 and 27 were being treated with insulin by Dr. R. Fitz and Dr. W. P. Murphy, but no definite effect of this treatment on the venous blood oxygen could be demonstrated. Patient 15 was given eight units of insulin immediately after the venous blood had been drawn, and samples were again taken forty-five minutes and two hours after the injection. The venous oxygen unsaturation showed a slight increase—12.61, 13.43, and 14.42 per cent. by volume in the successive samples.

According to Table 1, the patient's age, the presence or absence of detectable arteriosclerosis (many were examined ophthalmoscopically to try to detect sclerosis of the retinal arteries), the presence of obesity or emaciation, or the amount of sugar in the blood or urine apparently had no relation to the degree of oxygen unsaturation in the venous blood. In a general way, the longer the duration of the disease, the greater the oxygen unsaturation. Thus, of sixteen patients who had had diabetes for two years or less, only seven (44 per cent.) had a venous oxygen unsaturation greater than 8 per cent. by volume, while of fourteen patients with diabetes of longer than two years' duration, eleven (79 per cent.) had an oxygen unsaturation greater than 8 per cent. by volume. Two of the patients had evidence of chronic myocarditis, but both of them were compensated at the time of the determination, and both had an oxygen unsaturation lower than the average for the diabetic group.

3. Lundsgaard, C.: J. Exper. Med. **30**:147, 1919.

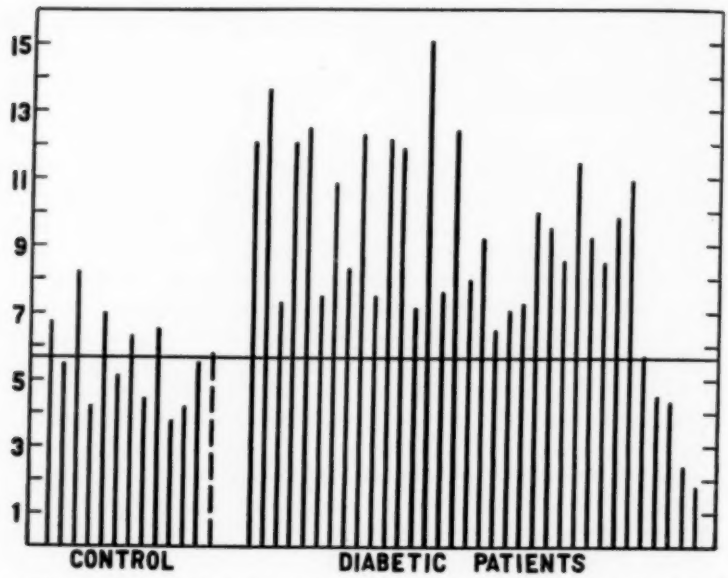

Fig. 1.—The vertical lines represent the oxygen unsaturation of the venous blood in per cent. by volume. The broken line in the control group represents the average normal found by Lundsgaard. The horizontal line is at the average height of the control group.

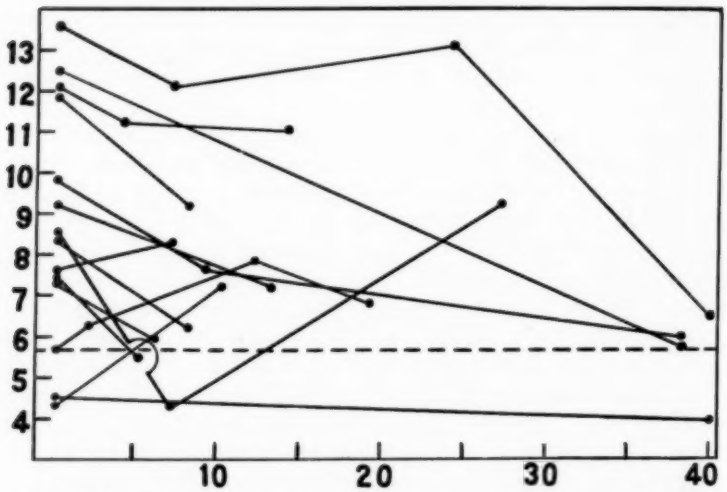

Fig. 2.—Venous oxygen unsaturation in per cent. by volume of fourteen diabetic patients who had two or more determinations during the course of treatment. The time is charted in days along the base line. The interrupted line indicates the average normal.

In Table 1 the collected clinical data concerning the patients is given. In Table 2 the data of the blood oxygen analyses and basal metabolism determinations is given, and in Table 3 data concerning the control subjects.

In reviewing the literature, it was found that Bondi and Mueller [4] in 1909 studied the systolic output of the heart by an arm plethysmograph method, and included seven diabetic persons among a group of

TABLE 1.—*Oxygen Unsaturation and Clinical Data in Patients with Arteriosclerosis and with Diabetes*

Patient	Age	Habitus	Duration of Diabetes	Arteriosclerosis	Sugar in Urine	Blood Sugar Percentage	Blood Pressure	Oxygen Unsaturation, % by Volume	Other Diagnoses
1	48	Normal	18 mo.	Slight	0	0.212	122/ 72	12.07	None
2	44	Obese	12 mo.	None	0	0.159	140/ 92	15.10	None
3	42	Normal	7 yr.	None	0	.....	120/ 84	7.15	None
4	39	Obese	30 mo.	None	0	0.177	116/ 80	12.39	None
5	65	Normal	12 mo.	Moderate	0	0.140	170/ 90	7.49	None
6	54	Normal	6 mo.?	None	0	0.130	155/ 99	7.97	Chronic myocarditis
7	66	Slight wasting	2 yr.	Slight	Trace	0.110	124/ 70	11.45	Neuritis
8	54	Normal	6 yr.	Moderate	0	0.080	240/130	9.10	Angina pectoris
9	38	Normal	?	None	0.8%	0.000	165/120	7.02	None
10	57	Wasted	2 yr.	Slight	0	0.250	124/ 72	4.57	None
11	43	Wasted	4 yr.	None	0.37%	0.160	142/100	1.80	None
12	71	Wasted	?	Definite	Trace	0.180	185/110	9.98	None
13	51	Normal	14 yr.	Slight	Trace	0.140	130/ 70	9.55	None
14	42	Normal	4 yr.	None	Trace	0.110	100/ 58	8.49	None
15	54	Slight wasting	3 yr.	Moderate	0	0.120	130/ 84	10.93	None
16	62	Wasted	1 yr.	Moderate	0	0.140	155/ 90	7.49	Active pulmonary tuberculosis
17	49	Obese	4 mo.	None	0	0.140	130/ 80	7.61	None
18	18	Wasted	4 mo.	Very slight	1.3%	0.290	118/ 80	4.56	Active pulmonary tuberculosis
19	13	Wasted	13 mo.	None	2.94%	0.250	85/ 45	8.58	None
20	48	Obese	?	Very slight	0	.....	150/125	6.45	Chronic myocarditis
21	36	Wasted	5 yr.	None	0.37%	0.190	110/ 75	9.22	Cataract
22	21	Wasted	18 mo.	None	....	0.230	92/ 72	7.24	None
23	23	Thin	3 mo.	None	1.2%	0.195	118/ 90	9.84	None
24	33	Wasted	14 mo.	Moderate	0	0.239	76/ 40	2.41	None
25	53	Obese	5 yr.	None?	0	0.174	148/ 98	11.87	None
26	52	Normal	5 yr.	Slight	0.75%	0.210	115/ 80	5.71	None
27	38	Wasted	9 mo.	Slight	0	0.336	100/ 64	12.50	None
28	28	Wasted	5 mo.	None	5.8%	0.253	105/ 70	7.32	None
29	50	Obese	3 mo.?	None	0	0.157	148/100	10.85	None
30	50	Wasted	4 yr.	Slight	0	0.195	128/ 80	12.36	None
31	60	Normal	3 yr.	None	0.10%	0.183	145/ 80	12.17	None
32	22	Normal	30 mo.	None	0	0.276	104/ 76	13.65	None
33	57	Obese	9 yr.	Moderate	0	0.151	165/ 80	12.06	Diabetic ulcer
34	62	Obese	?	Slight	0	0.265	134/ 60	8.36	Duodenal ulcer

other patients. By this method three of the seven diabetic patients had a smaller systolic output than normal. In 1922, E. Koch [5] studied the rapidity of the circulation by injecting a dye into the vein of one arm and noting the time before its appearance in the vein of the opposite arm. In the five cases of diabetes included among a large number of miscellaneous cases, the rate was slower than normal.

4. Bondi, S., and Mueller, A.: Deutsch. Arch. f. klin. Med. **97**:569, 1909.
5. Koch, E.: Deutsch. Arch. f. klin. Med **140**:30, 1922.

TABLE 2.—*Blood Oxygen Analyses and Basal Metabolism*

Patient	Oxygen Capacity, % by Volume	Venous Oxygen Content, % by Volume	Arterial Oxygen Content, % by Volume	Oxygen Unsaturation, % by Volume	Basal Metabolism Percentage	C.c. Oxygen Intake per Minute	Surface Area, Square Meters	Pulse Rate	Index of Blood Flow per Min., C.c.
1	21.52	9.45	20.45	12.07	— 4	240	1.82	68	1,199
2	22.98	7.83	22.08	15.10	— 1	285	2.11	91	886
3	20.37	13.22	19.57	7.15	+ 2	236	1.71	85	2,173
4	18.70	6.31	18.23*	12.39	+ 4	201	1.51	89	1,117
5	20.99	13.50	20.47*	7.49	— 6	220	1.83	78	1,725
6	20.53	12.56	20.40	7.97	+ 4	205	1.62	64	1,596
7	30.05	8.60	19.60	11.45	—24	161	1.64	82	893
8	17.78	8.58	17.34*	9.20	— 3	250	1.95	60	1,464
9	22.54	15.52	22.96	7.02	+12	286	1.81	90	2,101
10	18.57	14.00	18.62	4.57	— 1	170	1.38	86	2,667
11	16.49	14.69	16.11	1.80	—27	150	1.50	64	7,042
12	18.10	8.12	17.54	9.98	— 5	158	1.44	69	1,165
13	17.15	7.60	17.39	9.55	—13	188	1.64	50	1,171
14	17.40	8.91	16.96	8.49	—12	216	1.80	61	1,491
15	19.92	8.59	18.78	10.93	—14	206	1.81	55	1,085
2 days later	18.49	5.88	18.03*	12.61	—14	206	1.82	55	994
16	18.52	11.05	18.06*	7.49	(+10)†	(201)	(1.53)	..	(1,869)
3 days later	18.66	13.17	17.41	5.49	+10	201	1.53	77	2,444
17	20.92	13.32	20.40*	7.60	(— 6)	(204)	(1.70)	..	(1,200)
7 days later	19.13	10.80	17.96	8.24	— 6	204	1.70	74	1,705
18	18.11	13.56	17.51	4.56	+ 3	194	1.40	67	3,493
48 days later	17.17	13.22	16.93	3.95	— 5	175	1.38	87	3,418
19	17.95	9.37	17.95	8.58	—40	113	1.07	68	1,231
7 days later	16.75	12.39	16.75	4.36	—40	117	1.11	60	2,401
27 days later	14.88	5.59	14.80	9.29	—35	124	1.10	54	1,224
20	20.84	15.47	20.32*	5.37	+28	306	1.85	124	3,377
15 days later	20.65	14.29	20.13*	6.45	— 7	221	1.85	90	2,015
21	19.21	14.10	19.31	5.11	+13	249	1.57	75	3,044
12 days later	17.36	8.14	17.04	9.20	—16	183	1.57	57	1,310
25 days later	16.78	9.56	16.36*	7.20	—16	187	1.60	57	1,719
22	18.11	13.78	18.06	4.33	— 1	160	1.25	77	2,623
10 days later	17.68	10.44	17.58	7.24	— 6	159	1.28	74	1,740
23	19.71	9.87	19.22*	9.84	(—24)	(153)	(1.55)	..	(1,056)
9 days later	18.24	10.60	18.24	7.64	—24	153	1.55	59	1,292
40 days later	15.50	9.49	15.28	6.01	—21	157	1.55	67	1,750
5 mos. later	17.40	10.23	17.28	7.17	—25	141	1.47	68	1,361
24	18.68	16.27	18.21*	2.41	(—38)	(123)	(1.52)	..	(4,171)
9 days later	17.04	12.30	16.57	4.68	—38	123	1.52	54	1,922
40 days later	14.72	11.50	14.31	3.22	—20	154	1.52	61	3,605
50 days later	17.68	14.45	17.19	3.23	—15	157	1.49	65	3,846
5 mos. later	16.23	13.36	16.19	2.87	—13	168	1.59	95	3,957
25	18.97	7.10	18.50*	11.87	(0)	(261)	(2.10)	..	(1,060)
8 days later	18.95	9.77	17.86	9.18	0	261	2.10	67	1,536
26	19.61	13.90	19.12*	5.71	(—23)	(160)	(1.59)	..	(1,928)
2 days later	18.89	12.67	18.42*	6.22	(—23)	(160)	(1.59)	..	(1,750)
12 days later	17.73	9.92	17.31*	7.81	(—23)	(160)	(1.59)	..	(1,365)
20 days later	17.11	10.29	16.77	6.82	—23	160	1.59	63	1,553
27	16.68	4.18	16.26*	12.50	(— 1)	(206)	(1.48)	(74)	(1,152)
38 days later	16.87	11.10	16.45*	5.77	—12	188	1.65	64	2,267
28	19.00	11.77	18.61*	7.32	(— 4)	(204)	(1.53)	..	(1,960)
6 days later	19.49	13.53	19.00*	5.96	— 4	204	1.58	61	2,437
29	19.71	8.86	.....	10.85					
30	17.36	5.00	.....	12.36					
31	21.21	9.04	.....	12.17					
32	19.22	5.57	18.74*	13.65	(— 5)	(230)	(1.73)	..	(1,010)
7 days later	20.26	8.24	19.75*	12.02	— 5	230	1.73	51	1,155
22 days later	18.40	5.35	17.95*	13.05	(— 5)	(230)	(1.73)	..	(1,056)
5½ mos. later	17.91	11.41	17.46*	6.50	+ 9	272	1.78	62	2,526
6 mos. later	17.90	11.79	17.45*	6.11	— 9	227	1.77	57	2,266
33	19.68	7.62	.....	12.06					
4 days later	18.91	7.69	.....	11.22					
14 days later	18.76	7.78	.....	10.98					
34	20.98	12.62	.....	8.36					
8 days later	14.54	8.32	.....	6.22					

* The arterial blood was not obtained in these instances, but was assumed to be 97.5 per cent. saturated.

† The determinations of the basal metabolism were not always made each time blood samples were taken, in which case figures from other determinations on the same patient were used in the calculations. These figures are enclosed in parentheses.

In twenty-nine of the patients determinations of the basal metabolism were made, many of them in connection with a study of insulin being carried on by Dr. Fitz and Dr. Murphy. These determinations were made in duplicate by Miss G. Kauffmann, using the Tissot method, the expired air being analyzed in the Haldane apparatus, and the oxygen consumption per minute thus accurately ascertained. In these patients, immediately after the completion of the basal metabolism determination, while the patient was still under basal conditions, samples of blood were drawn without stasis and under oil from the anticubital vein and from the radial artery, and analyzed for oxygen content and oxygen capacity. I then indulged in the luxury of calculating a figure for the blood flow on the basis of these figures, realizing fully the fallacy of attempting to calculate the blood flow of the body

TABLE 3.—*Data Concerning Control Subjects*

Subject	Diagnosis	Oxygen Capacity, % by Volume	Venous Oxygen Content, % by Volume	Arterial Oxygen Content, % by Volume	Oxygen Unsaturation, % by Volume	Basal Metabolism Percentage	C.c. Oxygen Intake per Minute	Surface Area, Square Meters	Index of Blood Flow per Minute, C.c.
A.	Normal	20.62	16.39	20.84	4.23	0	235	1.68	3,143
K.	Normal	17.26	10.50	17.22	6.76	+11	218	1.53	2,120
E.	Normal	17.86	12.68	17.40*	5.17	— 9	167	1.38	2 828
G. W.	Normal	20.55	16.08	20.04*	4.61	— 7	246	1.92	3,244
C.	Arthritis	17.98	11.47	17.48*	6.46	+ 7	250	1.54	2,681
P.	Inactive pulmonary tuberculosis	20.23	14.71	19.38	5.52	+12	295	1.92	3,642
R.	Constipation	21.29	14.96	20.76*	6.33	— 6	232	1.73	2,545
J.	Acromegaly	17.51	13.73	16.98	3.78	+14	399	1.74	4,397
D.	Adenoma of thyroid	19.29	15.10	18.75	4.19	0	235	1.63	3,945
W.	Duodenal ulcer	18.18	9.94	18.53	8.24	— 4	236	1.83	1,501
S. E.	Normal	19.03	12.32	.....	6.71				
H.	Normal	18.41	12.88	.....	5.53				

* The arterial blood was not obtained in these instances, but was assumed to be 97.5 per cent. saturated.

by using factors in which the utilization of oxygen from blood in only one part of the body (the arm in this case) is included. The oxygen consumption was divided by the difference between the oxygen contents of the arterial and the venous blood, and, since the oxygen consumption is proportional to the surface area, the figure obtained was divided by the surface area in order to compare persons of different sizes more accurately. Naturally, the figures thus obtained did not actually represent the total blood flow. They may, however, represent a rough index of the volume of the circulation in the arm.

The results of these calculations showed a striking difference between the twenty-nine diabetic and ten control subjects. Of the diabetic persons, all but three had a figure for the blood flow which was lower than the average normal, and the average figure for all the diabetic persons was 1827 c.c., as compared with 3024 c.c. for the

normal subjects, a reduction of 40 per cent. (Fig. 3). Ten of the diabetic persons had a basal metabolism of from 17 to 40 per cent. below normal, with a correspondingly low oxygen consumption. This would account for part of the lowering of the figure in these ten subjects, but not entirely, because seven of them had a definitely increased oxygen unsaturation in the venous blood. Two of them, with basal metabolisms of — 38 and — 27, had oxygen unsaturations which were markedly lower than normal, so that the figure for the blood flow was actually greater than normal. The low metabolic rates in these patients were presumably due to the prolonged period of undernutrition.

Arteriosclerosis is undoubtedly the factor of prime importance in the producion of diabetic gangrene, but it is interesting to speculate

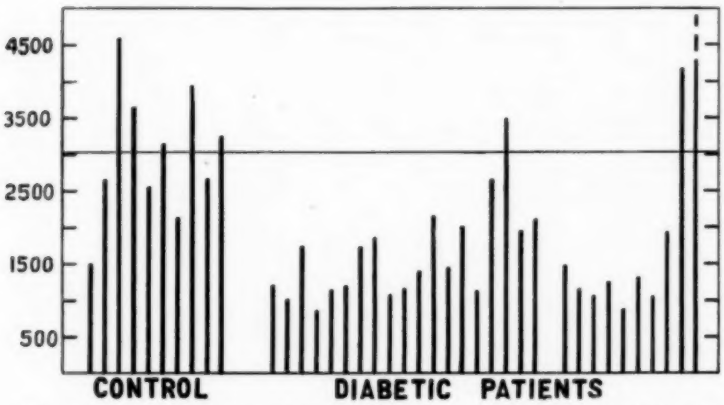

Fig. 3.—The vertical line represents the figures obtained in calculating the index of minute volume of blood flow in the arm. The horizontal line is at the average height of the control group. The group of diabetic patients at the extreme right is composed of those having basal metabolic rates from 10 to 40 per cent. below normal.

as to the possible relationship between the increased oxygen unsaturation, independent of arteriosclerosis, and the susceptibility of diabetic persons to gangrene and infections of all sorts.

SUMMARY

1. The average venous oxygen unsaturation of thirty-four diabetic patients was found to be 59 per cent. greater than the average normal.

2. This increase in the venous oxygen unsaturation would seem to indicate a slow blood flow through the arm in diabetic patients. However, this cannot be definitely stated to be true. The data concerning the blood oxygen is offered merely as an addition to the mass of slowly accumulating facts known about diabetes mellitus.

GASTRIC SECRETION IN RESPONSE TO DUODENAL FEEDING *

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The treatment of gastric diseases by duodenal alimentation attempts to put the stomach at rest from its motor activity, as well as from its secretory action. It became of interest to the writer to determine to what extent one can actually eliminate the function of the gastric epithelia. With this object in view, experiments by means of two duodenal tubes were begun on July 7, 1921, and continued to the present time. I mention this date, because recently Heller [1] employed the same principle for other work.

TECHNIC

The Einhorn tube was first allowed to pass into the duodenum in the usual way. After it was definitely proved in place and duodenal alimentation had been successfully carried out, another duodenal tube was swallowed, but not allowed to pass out of the stomach. It was at times difficult to have this second tube rest at the most dependent portion of the stomach. One must be certain that this is the case, as otherwise aspiration will not bring forth the secretions. At times it required the roentgen rays to visualize its proper position. Then, too, it is often necessary to change the posture of the patient from reclining to sitting, or vice versa, or from one side to another, to enable proper suction. A tight asbestos aspirating syringe is employed. In spite of all these precautions, complete emptying of the stomach by aspiration is well nigh impossible, because of the changing position of the tube.

DUODENAL ALIMENTATION

The feedings took place every two hours, and consisted of 7 ounces (200 gm.) of milk, two eggs, one-half dram (1.95 gm.) of lactose, one square of butter and a pinch of salt. The regular Einhorn duodenal outfit was used, and the aim was always that each feeding should not take less than twenty minutes. As a rule, seven feedings a day were given—at 8, 10, 12, 2, 4, 6 and 8 o'clock, and twice a day 500 c.c. of warm saline were allowed to enter the duodenal tube by the drip method.

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* Read at the American Gastro-Enterological Association, Atlantic City, April 30, 1923.

* From the laboratory and medical division of the Lenox Hill Hospital Service of Dr. J. Kaufmann.

1. Heller, E. P.: Employment of Two Duodenal Tubes in Gastro-Enterology, J. A. M. A. **80**:31 (Jan. 6) 1923.

REPORT OF CASES

CASE 1.—H. W., a salesman, aged 35, admitted to the service of Dr. J. Kaufmann at the Lenox Hill Hospital on June 29, 1921, had complained for five months of a burning feeling and bloated sensation in the epigastrium associated with acid eructations and belching. These disturbances would come on about an hour after eating and continue indefinitely until the next meal, when he would again be relieved for a short time by food. At night he had a gnawing pain in the pit of his stomach. The bowels were constipated. He had lost 16 pounds (7.25 kg.) in weight in five months. He was an asthenic type with a low blood pressure (systolic, 104; diastolic, 70). The urine was normal. A fractional analysis of the gastric contents was made after a Boas-Ewald test meal and showed hyperacidity (Table 2). Red blood cells were noted microscopically in the gastric contents. Roentgen-ray examinations were unsatisfactory, because the patient did not hold his breath properly.

TABLE 1.—*Result of Simultaneous Duodenal Feeding and Suction on the Gastric Tube*

	Amount of Gastric Juice Aspirated	Free Hydrochloric Acid	Total Acidity
Immediately after the first 25 c.c. of duodenal feeding	48 c.c.	46	58
15 minutes later	8 c.c.	58	74
30 minutes later	30 c.c.	62	76
45 minutes later	12 c.c.	18	40
1 hour later	14 c.c.	34	56
1½ hour later	14 c.c.	42	60
2 hours later	3 c.c.	25	50
	129 c.c.		

TABLE 2.—*Free Hydrochloric Acid and Total Acidity After a Boas-Ewald Test Meal*

	Amount	Free Hydrochloric Acid	Total Acidity
15 minutes after Boas-Ewald meal	20 c.c.	38	70
30 minutes after Boas-Ewald meal	42 c.c.	48	78
45 minutes after Boas-Ewald meal	29 c.c.	58	80
60 minutes after Boas-Ewald meal	17 c.c.	60	82

Duodenal alimentation was instituted, and on the third day, the second duodenal tube was passed into the stomach. Just before the time of a duodenal feeding 30 c.c. of pure gastric juice were aspirated. The feeding apparatus was then attached to the duodenal tube and feeding started. At the same time suction was applied to the gastric tube. To our surprise the entrance of the first 15 to 25 c.c. of the milk egg mixture into the duodenum was attended by a gush of gastric secretion, so that we were immediately able to aspirate 48 c.c. of pure clear watery gastric secretion. The duodenal feeding and the suction on the gastric tube were simultaneously continued, with the result shown in Table 1.

Thus it is observed that 130 c.c. of gastric juice was secreted during the two-hour period of duodenal feeding. If a similar gastric response (as is reasonable to assume from other experiments) were to take place during each feeding, seven times that amount, or approximately 1,000 c.c. of gastric juice would be secreted during the twelve hours of duodenal alimentation. The figures for free hydrochloric acid and total acidity in this secretion were almost as high as those of the gastric contents after a Boas-Ewald test meal, noted by fractional examination. It was made just after the patient's admission and is appended for comparison.

In order to show that this gastric response after duodenal feeding was not accidental or exceptional, eight additional examinations were made on different days at different times and at different intervals after the duodenal feedings, and at no time was the stomach found free of secretion. As is seen in Table 3, one could aspirate quantities varying from 3 to 75 c.c., and with acid contents as high as free hydrochloric acid 100 and total acidity of 110, figures much higher than those noted after the Boas-Ewald meal.

This patient suffered from an irritative form of gastric disorder, but of a moderate type and not the more marked form usually designated as alimentary hypersecretion.

TABLE 3.—*Secretion After Duodenal Feeding*

Hour of Duodenal Feeding	Time of Gastric Aspiration Before or After Duodenal Feeding	Amount of Secretion	Free Hydrochloric Acid	Total Acidity
July 13, 1921, 10 a.m. (milk-egg mixture)....	5 min. before	15 c.c.	8	28
11 a.m. (saline solution).....	30 min. after	10 c.c.	50	80
	50 min. after	30 c.c.	32	56
12 p.m. (milk-egg mixture)....	5 min. before	15 c.c.	80	100
	2 hours after	8 c.c.	40	68
	3½ hours after	3 c.c.	30	60
4 p.m. (milk-egg mixture)....	30 min. after	12 c.c.	66	88
	1½ hours after	13 c.c.	100	110
July 14, 1921, 8:10 p.m. (milk-egg mixture)..	25 min. after	45 c.c.	80	94
	50 min. after	30 c.c.	62	74
	1 hr. 30 min. after	22 c.c.	86	100
4 p.m. (milk-egg mixture)....	30 min. after	45 c.c.	80	94
10:30 a.m. (milk-egg mixture)....	30 min. after	75 c.c.	46	56
9:15 p.m. (milk-egg mixture)....	30 min. after	17 c.c.	56	60

TABLE 4.—*Findings After Employing the Two Tube Experiment*

Duodenal Feeding at 4 to 4:20	Amount	Free Hydrochloric Acid	Total Acidity
Gastric aspiration just before feeding.....	5 c.c.	0	20
Gastric aspiration at 4:30 p.m., 10 min. after.....	80 c.c.	52	66
Gastric aspiration at 5:00 p.m., 40 min. after.....	35 c.c.	40	62
Gastric aspiration at 5:30 p.m., 70 min. after.....	20 c.c.	56	74
Gastric aspiration at 6:00 p.m., just before next feeding	5 c.c.	0	4
Total.....	149 c.c.		
Duodenal Feeding at 6 to 6:20 p.m.			
Gastric aspiration at 6:30 p.m. showed.....	105 c.c.	46	60
Gastric aspiration at 7:00 p.m. showed.....	28 c.c.	30	42
Gastric aspiration at 7:30 p.m. showed.....	5 c.c.	60	70
Gastric aspiration at 8:00 p.m. showed.....	3 c.c.	4	8
Total.....	141 c.c.		

Similar experiments were repeated on another patient also with a moderate gastric secretion.

CASE 2.—A man, aged 54 years, suffered at varying intervals for eight years with burning pain in the epigastrium, which came on from one to three hours after eating and was relieved by taking food or bicarbonate of soda. In addition, he had acid eructations, heartburn, hiccups and frequent vomiting of sour material. He had lost 20 pounds (9 kg.) during his illness, but the greater part in the last three weeks. Roentgen-ray examination showed marked gastroptosis and deformity of the cap, which, however, was not constant. On aspiration three-fourths hour after the Boas-Ewald test meal, 151 c.c. of gastric contents were obtained, with a free hydrochloric acid reading of 31 and total acidity of 58.

As shown in Table 4, 149 c.c. of gastric secretion during the period of duodenal feeding from 4 to 6 p. m. and 141 c.c. during the period of feeding from 6 to 8 p. m. It is interesting to note that there was approximately the same type of gastric response to the same duodenal stimulation. It should be kept in mind for all these experiments that the total quantity secreted by the stomach might be even greater than the amount aspirated, because we applied suction only every half hour, and some gastric secretion probably passes through the pylorus during the interval.

That in this patient, too, the foregoing findings were not exceptional was corroborated at other times by passage of the second duodenal tube into the stomach; gastric secretion was always obtained.

TABLE 5.—*Findings After Passage of Second Duodenal Tube Into the Stomach*

Date	Time of Completed Duodenal Feeding	Interval After Feeding	Quantity	Free Hydrochloric Acid	Total Acidity
July 21, 1921	1:00 p.m.	10 min.	75 c.c.	58	88
	3:45 p.m.	15 min.	50 c.c.	80	94
	5:40 p.m.	15 min.	50 c.c.	84	100
	7:40 p.m.	15 min.	50 c.c.	40	54

The outstanding characteristic of the gastric secretion in response to the duodenal feeding is that it always commences with a gush almost immediately after the milk-egg mixture touches the duodenal mucosa.

In both cases cited, gastric secretion after the Boas-Ewald test meal was plentiful, although not excessive; this seemed to tally with a similar free response of the gastric glands to duodenal feeding. Two more such cases are quoted to prove that this reaction is not the exception.

CASE 3.—A woman, aged 21, an operator, came to the hospital complaining of gastric discomfort and gaseous distention after eating, which had existed for a year previous to admission. In addition, she suffered from occasional nausea and severe constipation. At times she had diffuse abdominal pains.

TABLE 6.—*Results of Two Tube Experiment*

Duodenal Feeding at 3 to 3:25 p.m.	Quantity	Free Hydrochloric Acid	Total Acidity
Gastric aspiration during 3 to 3:25 p.m....	80 c.c.	34	50
Gastric aspiration during 3:25 to 3:40 p.m.	40 c.c.	40	52
Total.....	120 c.c.		

Physical examination revealed only tenderness over the abdominal arterial nerve plexuses. Roentgen-ray examination showed no defects in the outline of the stomach, but the cap was irregularly although inconstantly deformed. Forty-five minutes after a Boas-Ewald test meal, 22 c.c. gastric contents were obtained with free hydrochloric acid 44 and a total acidity of 62. The patient was placed on duodenal alimentation. The results of the two tube experiment are given in Table 6.

No secretion could be aspirated after that[2] until following the next duodenal feeding at 5 p. m.

2. It is to be noted here as well as in repeated other tests that the mere presence of the tube in the stomach was not sufficient to stimulate gastric secretion.

Case 4.—A porter, aged 49, came to the hospital complaining of periodic attacks of heartburn and acid gaseous eructations of one year's duration. During the last two months they were more frequent. In addition he suffered from spells of nausea, headache and vertigo; also severe constipation. Physical examination was negative. Roentgen-ray examination revealed an irregularly and inconstantly deformed cap held close to the free border of the liver. Forty-five minutes after the Boas-Ewald test meal, 58 c.c. of gastric contents were aspirated with a free hydrochloric acid of 26 and a total acidity of 50. The results of a fractional examination after a Boas-Ewald test meal are given in Table 7.

The two tube experiment again showed a definite gastric secretion (of 172 c.c.) in association with the duodenal feeding.

It is interesting to note that in all of the cases cited there were moderate degrees of an irritative form of gastric disorder, which the next patient did not have.

Table 7.—*Results of Fractional Examination After a Boas-Ewald Test Meal*

	Quantity	Free Hydrochloric Acid	Total Acidity
Immediately after taking the test meal...	40 c.c.	44	60
15 minutes after.....	41 c.c.	42	54
30 minutes after.....	42 c.c.	46	62
45 minutes after.....	25 c.c.	36	50
1 hour after.....	34 c.c.	20	31
1¼ hour after.....	15 c.c.	20	31
Total.....	197 c.c.		

Table 8.—*Results of Two Tube Experiment*

Duodenal Feeding at 4:05 to 4:20	Quantity	Free Hydrochloric Acid	Total Acidity
4:05 to 4:20 obtained from stomach.....	60 c.c.	37	49
4:20 to 4:25 obtained from stomach.....	20 c.c.	44	56
4:25 to 4:30 obtained from stomach.....	35 c.c	50	62
4:30 to 4:40 obtained from stomach.....	10 c.c.	44	56
4:40 to 5:00 obtained from stomach.....	17 c.c.	52	62
5:00 to 5:20 obtained from stomach.....	30 c.c.	54	68
Total.....	172 c.c.		

Case 5.—A waiter, aged 30, admitted on Feb. 21, 1922, was highly neurotic and complained of vague symptoms of indigestion, belching of gases, sour eructations, slight pain in the left side, pain in the rectum and indefinite loss in weight. Physical and roentgen-ray examinations revealed no organic abnormalities. Forty-five minutes after a Boas-Ewald test meal only 12 c.c. of gastric contents could be aspirated, with free hydrochloric acid of 48 and a total acidity of 75.

Here, again, the gastric secretion responded in a similar way to both gastric and duodenal feeding: they both showed a small quantity of secretion.

Even more conclusive in this comparative respect were the findings in a case of achylia gastrica.

Case 6.—A clerk, aged 36, complained of cramplike pains in the epigastrium radiating to the left upper quadrant of the abdomen, without relation to meals; his appetite was poor; there was much discomfort after meals. Physical examination revealed no masses or tenderness; roentgen-ray examination

showed a deformed or absent cap in all the films. Forty-five minutes after a Boas-Ewald test meal, only 24 c.c. were obtained, with no free hydrochloric acid and a total acidity of 8.

The two tube experiment was carried out on May 25, 1922, three days after the Boas-Ewald test meal. The first duodenal tube was swallowed on May 24, about 9 p. m. The next morning the tube was in the duodenum, and duodenal feedings were given at 10 a. m., 12 and 2 p. m. Just before the 4 o'clock feeding the second tube was passed into the stomach, and suction yielded no secretion. Duodenal feeding was given from 4 to 4:25. Aspiration during

TABLE 9.—*Results of Two Tube Experiment*

	Total Amount	Free Hydrochloric Acid	Total Acidity
Aspiration at 8 a.m., just before feeding, showed	8 c.c.	0	22
Duodenal feeding 8 to 8:30			
Aspiration at 8:45	12 c.c.	0	42
Aspiration at 9:15	7 c.c.	16	74
Aspiration at 9:30	4 c.c	36	75
Aspiration at 9:50	10 c.c.	46	66
Total	33 c.c.		

TABLE 10.—*Results of Fractional Test Meal*

	Total Quantity	Free Hydrochloric Acid	Total Acidity
10 minutes after Boas-Ewald meal	30 c.c.	14	24
20 minutes after Boas-Ewald meal	34 c.c.	19	28
30 minutes after Boas-Ewald meal	44 c.c.	50	68
40 minutes after Boas Ewald meal	51 c.c.	56	74
55 minutes after Boas-Ewald meal	35 c.c.	80	94
1 hour after Boas-Ewald meal	38 c.c.	50	62
1 hour 15 minutes after Boas-Ewald meal	20 c.c.	40	50
1 hour 45 minutes after Boas-Ewald meal	36 c.c.	54	66
Total	288 c.c.		

TABLE 11.—*Gastric Juice After Duodenal Feeding*

	Quantity	Free Hydrochloric Acid	Total Acidity
10:13 to 10:15 (first 2 minutes)	48 c.c.	36	50
10:15 to 10:25 (first 10 minutes)	50 c.c.	76	88
10:25 to 10:35	50 c.c.	56	70
10:35 to 10:45	30 c.c.	46	58
10:45 to 11:00	50 c.c.	48	68
11:00 to 11:15	38 c.c.	54	68
11:15 to 11:30	15 c.c.	60	70
11:30 to 11:45	5 c.c.	4	20
Total	286 c.c.		

this whole time and for one hour after the feeding was stopped could bring forth absolutely no gastric juice in spite of continuous and drastic suction with the patient in various upright and reclining postures.

Most interesting and instructive were the experiments in a chronic ulcer patient with marked alimentary hypersecretion and hyperacidity. (Later the patient was operated on by Dr. Willy Meyer, and the condition proved to be a gastric ulcer.)

CASE 7.—The patient had been at the hospital on two occasions, the first time in January, 1918, and the last time in April, 1922. He had been suffering

periodically for about ten years from attacks which came on after shorter or longer intervals. During the upsets he would complain of pains and a gnawing or burning sensation in the epigastrium or right hypochondrium associated with gaseous eructations or regurgitations of burning acid fluids. These disturbances would come on several hours after eating and could be relieved by food or by bicarbonate of soda. He was often awakened at night because of these pains. During the attacks he lost weight. On several occasions the stools were dark. He was always tender to pressure in the epigastrium. Roentgen-ray examination in 1918 showed improper filling of the cap and periduodenal adhesions, and in 1922 there was distinct deformity of the last portion of the duodenum with fixation, also appendicular adhesions. A fractional test meal in April, 1922 (after two slices of toast and 8 ounces (250 gm.) of water) showed definite hypersecretion and hyperacidity.

A total quantity of 288 c.c. gastric contents were obtained, as shown in Table 10. Duodenal alimentation was instituted.

TABLE 12.—*Results of Later Duodenal Feeding*

12:15 stomach empty and duodenal feeding started	Quantity	Free Hydrochloric Acid	Total Acidity
12:15 to 12:20 aspirated from stomach....	45 c.c.	52	68
12:20 to 1:15 aspirated from stomach.....	156 c.c.	36	54
Total.....	201 c.c.		

TABLE 13.—*Results of Duodenal Feeding When Milk-Egg Mixture Was Put Into Stomach Through Tube*

9:50 to 10:00 feeding through stomach tube	Quantity	Free Hydrochloric Acid	Total Acidity	Description of Aspirated Fluid
10:00 to 10:10 aspirated....	45 c.c.	40	60	(⅞ milk, ⅛ whitish secretion)
10:10 to 10:20 by siphonage	90 c.c.	50	80	(½ milk, ½ whitish secretion)
10:20 to 10:30 by siphonage	38 c.c.	50	80	(⅓ milk, ⅔ whitish secretion)
10:30 to 10:45 aspirated....	13 c.c.	60	100	(All milky fluid)
10:45 to 11:00 aspirated....	46 c.c.	70	102	(½ milk, ½ whitish secretion)
11:00 to 11:15 aspirated....	57 c.c.	80	110	(⅓ milk, ⅔ whitish secretion)
11:15 to 11:30 aspirated....	19 c.c.	60	84	(No milk, all whitish secretion)
Total.....	317 c.c.			

The two tube method showed a surprisingly similar response in gastric secretion after duodenal feeding of the milk-egg mixture (April 21, 1922).

At 10:13 a. m. the stomach was aspirated, but no secretion was obtained. Duodenal feeding was started, and, just as in the former experiments, there was at once a gush of pure gastric juice.

As shown in Table 11, a total gastric secretion of 286 c.c. in response to 7 ounces (200 gm.) of duodenal alimentation, while the same amount of gastric juice was stimulated by taking two slices of toast and a cup of tea by mouth.

That this particular cycle of secretion was not exceptional was proved at a later duodenal feeding.

During the last period (12:20 to 1:15) the end of the duodenal tube, which rested in the stomach, was allowed to hang into a bottle placed at a lower level than the patient, and the gastric juice was allowed to drain out by gravitation instead of being aspirated. It is noted that in this way only 201 c.c. were collected, while with frequent suction 286 c.c. were aspirated. Possibly the difference passed into the duodenum.

The first quantity of gastric secretion, 286 c.c., stimulated by duodenal feeding, was so surprisingly profuse that it was thought interesting to compare

how much gastric secretion would be stimulated when the milk-egg mixture was put directly into the stomach through the tube rather than into the duodenum.

A total of 317 c.c. gastric contents were obtained, as shown in Table 13. This figure might have been a little higher because some of the gastric contents were evacuated into the duodenum. But, taking even this factor into consideration, the 317 c.c. represented less gastric secretion than was obtained after the duodenal feeding, because the 317 c.c. included approximately 220 c.c. of the original milk-egg mixture.

CONCLUSIONS

It is evident that one cannot put the stomach at rest from secretion by duodenal alimentation alone. None of my patients used alkalis by mouth or any other medication during the experiments. There seems to be a definite cycle of gastric secretion which starts just as soon as food enters the duodenum, and which depends on the type of patient we are dealing with. The greater the response of the secretory mechanism of the stomach to food intake by mouth, as in cases with hypersecretion, the greater also will be the gastric response to duodenal alimentation; the less the gastric response to food in the stomach as in some cases of achylia, the less gastric secretion in response to duodenal alimentation.[3] There are several factors which have been found to influence this reaction of the stomach to duodenal feeding, but they will be taken up in another paper. The exact physiologic mechanism whereby this reflex is brought about is still to be determined.

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3. It is interesting to make a comparison with the findings of Dr. McClure. He noted that the enzyme concentration of the pancreatic secretion in response to various types of foods was the same, no matter whether the feeding was into the stomach or duodenum. (Paper read at the meeting of the American Gastro-Enterological Association.)

DIGITALIS ELIMINATION *

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The fate of the digitalis bodies in the animal organism is one of the most interesting, though perplexing, problems in the study of this group of drugs. The more basic questions of digitalis action that inevitably arise in a consideration of such phenomena as tolerance, cumulation, difference in persistence, actions and effects, are imperfectly understood. A large literature has accumulated; still our knowledge is fragmentary, the evidence often contradictory, having been obtained under a variety of experimental conditions in different animals with different digitalis bodies.

Efforts to recover the digitalis bodies from hearts poisoned by them have been quite consistently negative.[1] While they cannot be recovered from living heart muscle brought to a standstill, they can be recovered from incubations of the drug with emulsions of the heart muscle.[2] The recovery of the largest part of the drug from the supernatant fluid of these incubations would contradict the observation that heart muscle contains a substance with a specific affinity for these glucosides.[3] There seems to be no evidence that these drugs are absorbed by the heart to any greater extent than by other tissues.[4] There is abundant evidence, however, both clinical and experimental,[5] that the heart is more susceptible to these drugs than other tissues. Perfusion experiments have shown that minute reduction in the concentration of the perfusion fluid occurs in passage through hearts.[6] Whether these quantities are fixed or destroyed by the heart is unknown.

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* From the Department of Pharmacology of Cornell University Medical College.

1. Cloetta, M., and Fischer, H. F.: Ueber das Verhaltens des Digitoxins im Organismus, Arch. f. exper. Path. u. Pharmakol. **54**:294, 1906. Straub, W.: Quantitive Untersuchung des Eindringens von Alkaloiden in Lebende Zellen, Arch. f. d. ges. Physiol. **98**:233, 1903. Hatcher, R. A.: The Absorption, Excretion, and Destruction of Strophanthin, Am. J. Physiol. **23**:303, 1908. Clark, A. J.: The Factors Determining Tolerance of Glucosides of the Digitalis Series, J. Pharmacol. & Exper. Therap. **4**:399, 1912.

2. Cloetta and Fischer, and A. J. Clark: Footnote 1.

3. Schliomensun, B.: Ueber die Bindungsverhältnisse zwischen Herzmuskel und Digitalis, Arch. f. exper. Path. u. Pharmakol. **63**:294, 1910.

4. Hatcher, R. A.: Footnote 1. Clark, A. J.: Footnote 1.

5. Fraser, T. R., and Mackenzie, A. T.: Strophanthus Sarmentosus; Its Pharmacologic Action and Its Use as an Arrow Poison, Trans. Roy. Soc., Edinb. **47**:341, 1910.

6. Clark, A. J.: The Influence of Ions upon the Action of Digitalis, Proc. Roy. Soc. Med. Therap. & Pharm. Sect. **5**:181, 1912. Straub, W.: Quantitativ Untersuchungen über den Chemismus der Strophanthinwirkung, Biochem. Ztschr. **28**:392, 1910.

The largest part of ouabain or digitoxin is eliminated from the blood stream in a few minutes.[7] There is evidence that their disappearance from the body is determined in part by destruction, in part by elimination through the bile [8] and the urine.[9]

Studies concerned with the estimation of the drug in the heart, in the remaining tissues and in the excreta have yielded in the main only qualitative information. The problem has been approached from another standpoint, namely, elimination has been determined in terms of persistence of action. By such a study, Hatcher,[10] though not attempting to establish the precise curve, about ten years ago, was able to show that the so-called cumulative action of digitalis was dependent on the persistence of action of previous doses, and that the persistence of some digitalins was considerably longer than that of others. He considered his results as affording a starting point for a reinvestigation of the subject of persistence and cumulation. Certain important questions remained unanswered, namely, (1) whether different specimens of digitalis are eliminated at the same rate, and (2) the nature of the line or curve of elimination. No subsequent work, either clinical or experimental, has investigated these problems. This paper is concerned with a report of the results obtained in a study of the rate of digitalis elimination in terms of persistence of action.

METHOD

Over 200 experiments were performed on the cat with the following preparations: three tinctures of digitalis, one specimen of digitoxin, one preparation of digitalis, made a year previously, consisting of the fraction left after ether extraction, and one commercial specimen that had been found to be rapidly eliminated. The activity of each preparation was first determined in the usual manner in terms of the cat unit.[11] With few exceptions, 75 per cent. of a cat unit per kilogram of body weight was injected by vein. Freshly prepared ouabain solution 1:250,000 was then injected slowly into the vein at different intervals following the initial dose. The persistence of action in the case of each

7. Hatcher, R. A.: The Elimination of the Digitalis Bodies, J. A. M. A. **61**:386 (Aug. 9) 1913.

8. Hatcher, R. A., and Eggleston, C.: Studies in the Elimination of Certain of the Digitalis Bodies from the Animal Organism, J. Pharmacol. & Exper. Therap. **12**:405 (March) 1909. Hatcher, R. A.: Footnote 1.

9. Cloetta and Fischer: Footnote 1. Hatcher and Eggleston: Footnotes 1 and 8.

10. Hatcher, R. A.: The Persistence of Action of the Digitalins, Arch. Int. Med. **10**:268 (Sept.) 1912.

11. Hatcher, R. A., and Brody, J. G.: Biological Standardization of Drugs, Am. J. Pharm. **82**:360, 1910.

preparation was determined at intervals of three hours, one day, two days, three days, four days, and then at intervals of four days as long as persistence was exhibited.

Protocol of a Typical Experiment.—4/4/23 Cat: Male; weight, 2.66 kg. Phenol for local anesthesia. 10:43, injected 75 per cent. cat unit per kg. by vein (3.99 c.c. total). 10:45, licks repeatedly. 10:57, emesis.

4/6/23 Animal slightly depressed. Weight, 2.48 kg. 11:15, began injection of ouabain solution 1:250,000. 12:00, convulsion; death.

Time: 45 minutes. Total: 25.5 c.c. injected.

Calculation of Elimination.—The matter of calculation presented some difficulties. First, as the cat unit is based on the average of several experiments, that 75 per cent of the calculated fatal dose should be fatal to some was inevitable. Second, as the standard cat unit had been established on animals under the ordinary conditions of feeding and in the average state of nutrition, one could not say whether the cat unit of 0.1 mg. ouabain would apply to animals that had been starved several days (toxic doses of digitalis producing such marked and prolonged digestive upset that the animal would for days eat little or nothing and lose considerable weight). Third, the calculation would show considerable difference depending on whether the original or the new weight on the day of the ouabain injection was used.

We cannot be absolutely certain that the method is correct in all details; in fact, we are aware of unavoidable flaws. Nevertheless, we feel quite certain of the general principles, the validity of which is supported in part by facts, in part by rational assumptions. That the cat unit based on the average of several experiments is a constant, has been repeatedly demonstrated. Therefore, the animals in which 75 to 80 per cent. of a cat unit was fatal, were considered more susceptible than the average; the remaining animals more tolerant than the average. The cat unit was then readjusted for either the remaining animals of that series, or, as in one case, for the remaining animals used with that preparation. Deaths after the first day were entirely omitted from the calculation.

Second, to determine whether starvation altered the fatal dose, a number of animals were starved over a certain period of time, after which they were killed by the slow intravenous injection of ouabin solution 1:250,000. The results are given in Table 6. From the quantity of ouabain necessary to kill after starvation, the fatal dose per kilogram was determined on the basis of the original, the new and the mean of the two weights. It is evident, from the data, that the old weight brings the fatal dose as far below the cat unit as the new weight brings it above, and that the fatal dose equals the standard cat unit of 0.1 mg. ouabain if the mean of the original and the new weights is taken.

Incidentally, we might note that the fatal dose rises for a time at least with the period of starvation and the percentage of weight lost. It is also rather interesting that on the basis of the original weight, Animal 3 is more susceptible than Animal 4; on the basis of the new weight, their susceptibility is reversed, corresponding to the greater loss of weight in Animal 3. A similar tendency to a greater rise in the fatal dose corresponding to the greater loss in body weight is also seen in Animals 1 and 2. This phenomenon is prabably due to the loss of gastro-intestinal contents, fluid and other body substance that normally take up no drug, but affect in lowering the fatal dose per kilogram by their weight.

To calculate the percentage of elimination, the amount of ouabain actually required to kill after the interval following the initial injection is subtracted from the amount theoretically, required to kill an animal weighing the average of the original and the new weights, the result representing the amount of digitalis in the body. The latter subtracted from the amount given in the

original injection (the ouabain equivalent of 75 per cent. cat unit of digitalis) gives the quantity eliminated, which, in turn, divided by the amount given in the initial dose yields the percentage of elimination.

Example of a Complete Calculation.—The quantities are all expressed in terms of ouabain. Sixty animals used with preparation—their average theoretic cat unit,0.1 mg.; 23 animals died with 75 to 80 per cent. of theoretic fatal dose—their average cat unit, 0.0769 mg.; 37 animals remaining—their average cat unit, 0.114 mg.

Cat 1; original weight, 3.44 kg; new weight, 3 kg.; mean weight, 3.22 kg. Amount required theoretically to kill = 0.326 mg. (3.22 kg. × 0.114). Amount required actually to kill after twenty-four hours =0.181 mg. Therefore, amount in body after twenty-four hours = 0.145 mg. (0.326 — 0.181). Amount given in original dose = 0.258 mg. (75 per cent. cat unit per kg.) 0.258 mg. — 0.145 mg. = 0.113 mg., quantity in body after twenty-four hours. 0.113 ÷ 0.258 = 42.1 per cent. elimination in twenty-four hours.

TABLE 1.—*Percentage of Elimination* *

Interval in Days	3 Hours	1	2	3	4	8	16	22
	15.1	15.6	37.6	18.7	1.3	37.0	49.2	40 0
	19.4	24.6	40.2	26.0	35.0	49.5	64.3	70.8
	22.6	29.0	50.0	30.6	52.8	67.0	68.2	86.5
	100.0	31.3	58.3	31.2	58.5	100.0	100.0	100.0
	.....	57.5	60.0	42.7	68.8	.....	.....	.....
	.....	....	60.8	70.0	....	.....	.....	.....
Averages	19.0	31.6	50.3	36.5	62.4	63.4	70.4	74.3

* The specimen used was tincture digitalis prepared from German leaf. The activity was 68 mg. per cat unit. The following were omitted from the final averages: Animal 4 of the three hour series, Animal 1 of the four day series. About 38 per cent. of the animals with this preparation died a few minutes after the initial injection; the remaining ones became 15 per cent. tolerant (see method of calculation). It is possible that this procedure prolongs the curve of elimination somewhat beyond the actual limit. Of the animals that did not die a few minutes after the initial dose, 26 per cent. died from two to twelve days later, some showing evidence of infection, many showing no such evidence.

TABLE 2.—*Percentage of Elimination* *

Interval in Days	3 Hours	1	2	3	4	8
	45.5	60.0	51.7	62.4	100.0	....
	57.5	64.7	42.4	44.0	97.4	....
	12.8	78.9	48.2	99.9	79.4	....
	100.0	48.7	79.0	....	.....	....
	.....	25.0	57.5	....	.....	....
	.....	13.5	53.9	....	.....	....
	.....	....	92.3	....	.....	....
Averages	54.0	55.46	50.8	67.1	92.9	....

* The specimen used was tincture digitalis made from a commercial leaf (source not determined). The activity was 140 mg. per cat unit. The following were omitted from the final averages: Animal 6 of the one day series. Animals 4 and 7 of the two day series. With this specimen, about 25 per cent. of the animals (eight out of thirty-one) died in a few minutes after the initial injection. The cat unit was readjusted for the remaining animals of each series wherever necessary (see method of calculation). No animals with this specimen died after the first day from the initial dose.

The results, then, are expressed as percentage of elimination of the dose injected, the final figure for each interval representing the average of three to nine experiments. It will be seen that certain experiments are omitted from the final results because of apparent tolerance or susceptibility out of all proportion to that of the remaining members of the series, in other cases, because of the atypical behavior of the animal. On the other hand, some irregular results were not omitted from the final because by their inclusion the average did not depart to any considerable extent from the percentage of elimination of the majority and more consistent animals.

COMMENT

An examination of the data presented in Tables 1 to 5 will undoubtedly raise the question whether any information as to the general behavior of digitalis persistence can be obtained in view of such marked,

TABLE 3.—*Percentage of Elimination* *

Interval in Days	3 Hours	1	2	3	4	8
	25.2	50.0	100.0	92.0	72.9	100.0
	26.0	53.1	100.0	82.8	72.6	100.0
	57.9	71.0	100.0	61.8	53.8	85.7
	77.1	24.6	100.0	53.4	....	....
	11.3	100.0	100.0	71.2	....	....
	....	....	95.3	....	....	....
	....	....	85.7	....	....	....
	....	....	51.8	....	....	....
	....	....	50.0	....	....	....
Averages	41.9	59.7	86.9	72.4	66.4	95.0

* The specimen used was tincture digitalis prepared from a German leaf. The activity was 77.6 mg. per cat unit. With this specimen about 8 per cent. of the animals (two out of thirty-six) died a few minutes after the initial injection. The cat unit was readjusted for the individual groups wherever necessary (see method of calculation). About 13 per cent. (five out of thirty-six) of the animals died from two to six days after the initial injection. In some of the latter, the symptoms following the initial dose betrayed susceptibility greater than the average; in others, no such susceptibility was discerned.

TABLE 4.—*Percentage of Elimination* *

Interval in Days	3 Hours	1	2	3	4	8
	25.0	81.8	65.5	79.7	100.0	....
	28.3	82.2	66.6	79.4	92.7	....
	44.8	83.9	66.5	64.6	82.6	....
	55.2	83.6	58.1	44.5	....	....
	....	100.0	100.0	29.9	....	....
	....	67.5	26.3	100.0	....	....
	....	49.4	....	....	....	....
	....	24.0	....	....	....	....
	....	12.4	....	....	....	....
Averages	38.3	78.2	63.6	64.8	91.7	....

* The specimen used was a fraction obtained after ether extraction made about a year previously from a specimen of digitoxin-Keller. The activity was 0.255 c.c. per cat unit. With this specimen, only one animal died in a few minutes after the initial dose. About 6 per cent. (two out of thirty-one) died from one to four days after the initial injection. The three animals of the four-day series showed slight depression with the first injection. A dose of 100 per cent. of the fatal was then given to another animal (G). On the following day, it showed considerable depression; it died four days after the injection. Animal 6 of the three-day series showed peculiar tremors involving the entire body when it was put on the board on the second day after the initial injection. These nervous symptoms persisted for several hours. On the following day, it took over 100 per cent. of the theoretic fatal dose of ouabain to kill.

TABLE 5.—*Percentage of the Fatal Dose Necessary to Cause Death*

Interval in Days	1	2	3	4
	77.8	89.4	46.3	96.2
	94.9	51.0	54.3	84.8
	92.8	59.5	59.5	75.2
	76.8	57.1	87.5	....
	51.0	39.5	96.9	....
	35.2	....	....	....
Averages	71.0	58.5	68.8	84.5

Digitoxin-Merck

apparent individual variations. It was common experience in Hatcher's [10] study, as also in the present one, to find that one animal would eliminate apparently more in one day than another would in two or three days after receiving a similar dose of the same preparation.

Though individual variations are an attribute of any biologic work, we were not altogether unconcerned about this question until results were examined more carefully in the light of fuller data. Care has been taken to refer to these variations, in part at least, as apparent. It must be remembered that the calculations have been made on the basis that susceptibility is the same for each animal. Therefore the data seem to indicate that individual differences are solely those of elimination. The cat unit of the animal in which elimination is being determined is, of course, an unknown factor. That the cat unit of individuals vary is certain; that the average of several experiments is generally a constant is equally certain. So far, then, as variations in the final results are dependent on susceptibility, the averages approach a constant. It is quite probable that both factors, elimination and susceptibility, account for the individual differences. At all events, after making allowance for occasional variations that disturb the results of a series, it is evident that the behavior of the majority and more consistent animals

TABLE 6.—*Effect of Starvation on Fatal Dose*

Animal	Weight Lost, Per Cent.	Starvation Time	Fatal Dose on Bases of Weight		
			Old	New	Mean
1	14.5	6 days	0.0941	0.1100	0.1016
2	17.8	6 days	0.0774	0.0941	0.0849
3	25.8	10 days	0.0837	0.1305	0.1020
4	21.9	10 days	0.0945	0.1210	0.1041

approaches rather closely the average elimination obtained for the various intervals.

The relation of susceptibility to elimination has a bearing on this question. Many observations have been made which show that difference in tolerance of different species to strophanthin expresses a degree of tissue immunity.[12] Considerably greater quantities of the drug are necessary to affect the hearts of species known to be tolerant than of those known to be susceptible. Clark [1] says that tolerance to strophanthin offers an interesting contrast to that of atropin; with the latter drug, tissue immunity does not obtain, tolerance being determined by the capacity for absorption and destruction by the liver. Tissue immunity does not, however, seem to be the only explanation of differences in susceptibility of individuals of a species. After a short interval following the initial injection of 75 per cent. of the fatal dose, an occasional animal would take 20 per cent. or more above the full theoretic fatal dose of ouabain. That this animal is more tolerant than the average, we know. That it has eliminated practically all of the original

12. Evans, C. L.: Toxikologische Untersuchungen an bioelektsrischen Strömen, Ztschr. f. Biol. **59**:397, 1912. Clark, A. J.: Footnote 1.

dose, we assume. We are still aware that the animal might conceivably have been tolerant also to the extent of a considerable portion of the initial dose and, therefore, may have really eliminated little or nothing. It does not seem probable. It appears likely that the converse of this reasoning applies to those cases in which the sum of the initial and final dose after the interval is less than the average fatal dose.[10] The fact, together with the assumption, therefore, would indicate that tolerance to the digitalis bodies is in part, at least, measured by the capacity for elimination. They confirm the observation of Hatcher [10] that different species of animals—the cat, the dog and the rabbit—are tolerant to digitoxin in proportion to their capacity to eliminate it. However, one is led to suspect that this is not always true from the occasional occurrence of a rather severe reaction from the initial dose in an animal which after the interval showed greater elimination than the other members of the series that were less effected by the initial injection.

PERSISTENCE OF ACTION VERSUS ELIMINATION

The terms "elimination" and "persistence of action" have been used interchangeably. The results have been expressed as percentage of elimination of the dose injected. Lest the word "elimination" obscure the true nature of the determination, let us again state that the results express elimination of activity and not of the drug. Although ouabain and digitoxin apparently produce similar effects, those of the former disappear rapidly while those of the latter disappear slowly. Hatcher [10] suggested that this shows a difference in capacity for eliminating the two drugs. Eggleston,[13] on the basis of a clinical investigation, expressed a similar opinion for the same reason, deducing further that the persistence of digitalis expresses, not the "lasting effects of any injury to the heart," but the "actual presence of the drug in the tissues." This conception led the latter to the view, expressed also by an earlier investigator,[14] that the phenomenon of so-called cumulation represents simple storage of small fractions of previous doses fixed in the tissues.

These deductions make inevitable the conclusion that the curve of elimination of the drug and of its persistence of action should coincide. The diagrams show, with digitoxin, also rather consistently with tinctures of digitalis, a tendency to greater elimination after one day than after two or three days. That an animal could eliminate more drug in the first day than in the first two or three days is quite inconceivable, of course. That the drug might diffuse rapidly into the tissues, to be subsequently returned to the circulation and exhibit thereby a greater

13. Eggleston, C.: Clinical Observations on the Duration of Digitalis Action, J. A. M. A. **59**:1352 (Oct. 12) 1912.

14. Van der Heide, W.: Ueber die Kumulative Wirkung des Digitalins und Helleboreins, Arch. f. exper. Path. u. Pharmakol. **19**:127, 1885.

action on the second or third day than on the first, is a possibility. That a certain dose producing a given action might simply exhibit a greater effect on the second or third day than on the first seems less abstruse. However this may be, also irrespective of the nature of digitalis action, whether by chemical union with heart tissue in a quantity or manner not discernable by ordinary extraction, or by alteration of the physical state of the cells without such union,[15] it appears that the curves of effects and elimination of the drug from its seat of action do not run strictly parallel; it appears probable, therefore, that digitalis can produce an effect that persists independently to a degree, at least, of the presence of the drug.

This rise in toxicity did not occur with the commercial preparation that was practically completely eliminated in from three to four hours.

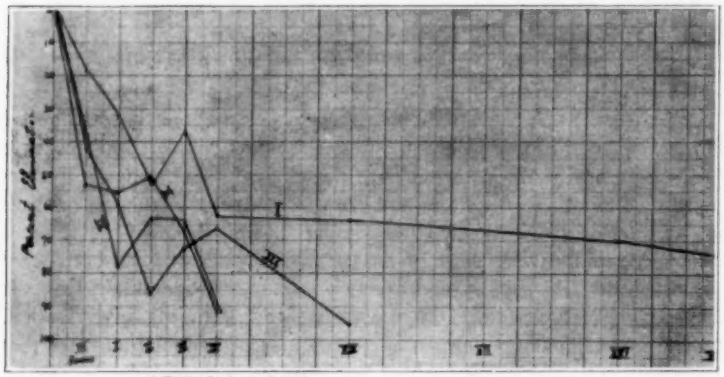

Diagram 1.—Curves of elimination for the preparations of digitalis employed. The numbers on the curves refer to the corresponding Tables 1 to 4.

Also after an interval of two days, six animals failed to show any evidence of persistence of action of the drug. The rise in activity occurred with our specimen of digitoxin, which showed considerable persistence after the same length of time. On the basis of the assumption that the capacity for eliminating the different digitalis bodies is not the same, we must conceive that the effect is not entirely independent of the presence of the drug. One might say, therefore, that a dose of a digitalis body produces an effect that increases with the persistence of the drug at its seat of action; this phenomenon gives rise to the increasing intensity of effect (Charts 1 and 2) when little or none of the drug has been eliminated, and prolongs the curve of elimination when the drug begins to disappear.

15. Straub, W.: Footnote 6.

The procedure with digitoxin differed somewhat from that with the other preparations (Table 5). We were interested mainly in the phenomenon of rising toxicity with digitalis, which, there was reason to suspect might be due to digitoxin. As it is rather difficult to establish the exact fatal dose of digitoxin, a toxic dose—0.2 mg. per kilogram—

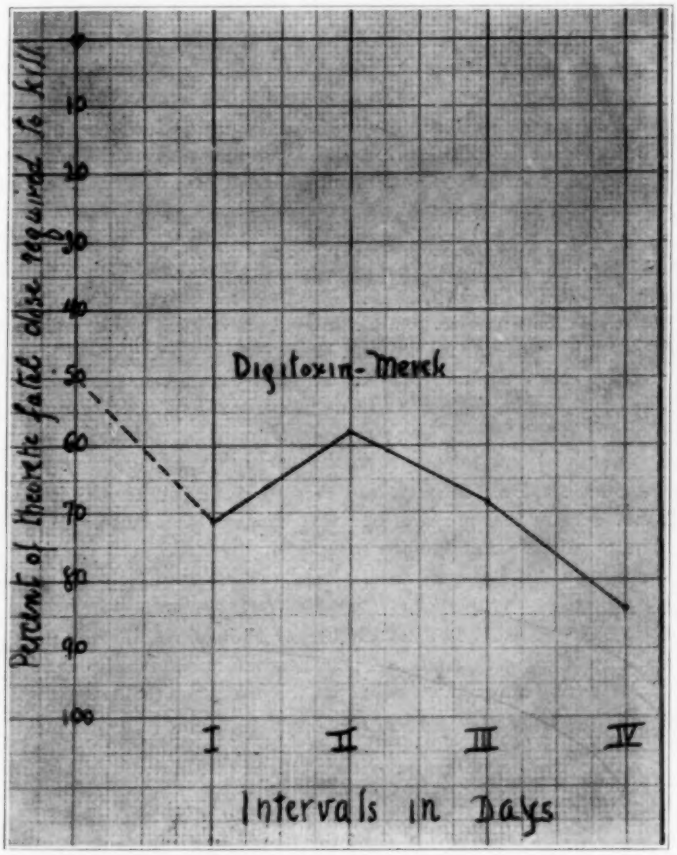

Diagram 2.—Curve of persistence of action for the specimen of digitoxin (Table 5).

was injected by vein. After the intervals, the injections were completed with ouabain solution and the results expressed as percentage of the fatal dose required to kill. One therefore does not know how much, if any, of the digitoxin was eliminated during the first day. After twenty-four hours, the animals took an average of about 70 per cent. of the

fatal dose of ouabain to kill. If none was eliminated, our initial dose of 0.2 mg. was only about 30 per cent. of the fatal dose. But since 0.3 mg. was almost fatal to two animals, it seems safe to assume that about 0.4 mg. was the fatal dose of our specimen of digitoxin. It seems probable, therefore, that there is at first a somewhat rapid descent of action, to show which we do not have the necessary data. It is indicated in Chart 2 by the broken line. This determination was not made because of the difficulty, as stated, of obtaining the exact fatal dose of digitoxin, also because our purpose was well served without it. It is plain that a given dose of digitoxin produces a greater effect on the second than it does on the first day.

The curve (Chart 2) does not show complete elimination after four days; yet the apparently slight persistence of digitoxin action after that interval seemed rather striking against the accepted notion about this digitalis body. Digitoxin has been considered one of the most persistent of the digitalis principles. That pure digitoxin crystals are not easily prepared is seen from Schmiedeberg's description,[16] in which he states also that he was able to obtain only from 2 to 2.5 gm. of the pure crystals from 20 kg. of the leaf. Although Schmiedeberg has shown that Nativelle's crystalline digitalin was a mixture consisting mainly of digitoxin, the name of this mixture is used as a synonym for digitoxin. While Merck's crystalline digitoxin is considered of most constant activity, it is apparent that one cannot be absolutely certain that the product employed is pure, and therefore one cannot be certain the behavior of any two preparations will be exactly alike.

The apparently rapid disappearance of digitoxin action was tested by the injection of the same dose, 0.2 mg. per kilogram by vein, repeated every four days. One animal (*A*) died thirty minutes after the third injection, having vomited after the first two, but not following the third dose. It took altogether 0.6 mg. per kilogram in a total period of eight days. A second animal (*B*) behaved similarly after the first two doses. Two minutes after the third injection, saliva began to drool, but there was no emesis. It began to show peculiar nervous symptoms; the entire body was limp; there was marked incoordination, the animal occasionally jumping with the hind legs together like a rabbit; there was a side to side movement of the head; it lapped milk; its expression seemed playful. These symptoms improved on the following day, but depression set in; the heart became very slow and irregular; it died four days after the last injection.

It is difficult to reconcile the facts shown by these two experiments with the apparently slight persistence shown by the combined ouabain

16. Schmiedeberg, O.: Untersuchungen über die pharmakologischwirksamen Bestandtheile der Digitalis purpurea L., Arch. f. exper. Path. u. Pharmakol. **3**:16, 1875.

method. The three repeated doses produced effects that could not be entirely accounted for by simple addition. The apparent contradiction of the two results points to a potentiation of effects of repeated doses of digitoxin, so that while recovery in many animals, to a large degree, may occur in four days after the single dose, the effects of repeated doses are not so rapidly recovered from.

The nervous phenomena noted in this animal have not been frequently referred to, although an action on the central nervous system by the digitalis bodies is recognized. The white rat is known to exhibit nervous symptoms with digitoxin resembling strychnin poisoning.[16] Nervous symptoms were observed to some degree in animals receiving a single dose of digitoxin, but little attention was paid because they seemed much like the temporary depression associated with nausea. With repeated injections, however, as noted above, the incoordination and general weakness were considerably more pronounced and seemed to obtain while the animal lapped milk and appeared playful. Potentiation may in part explain so-called cumulation in the effect of digitoxin on the heart as well as on the central nervous system.

One specimen of tincture of digitalis (Table 3) showed slight persistence after two days. This was confirmed by the repeated daily injection into the vein of 50 per cent. of a fatal dose into two animals. One animal (*C*) died about four hours after the fourth dose; the second animal (*D*) died about five minutes after the fifth dose. This elimination is rather striking compared with digitoxin persistence, in which case the third dose at intervals of four days was fatal.

If an animal could recover from the effects of a smaller dose more rapidly than from those of a larger one of the digitalis bodies, its behavior would be similar to that toward many other drugs. Two animals received daily injections by vein of 25 per cent. of the fatal dose of the tincture (same specimen as used in Table 3). One (*E*) died several hours after the eleventh dose; the other (*F*) died several hours after the tenth dose. These results do not show that small repeated doses are more rapidly eliminated than larger ones given in the same way. On the contrary, they point to the conclusion that the longer small doses are repeated the relatively greater persistence they show, confirming the possibility observed with digitoxin that repeated doses sensitize the heart to subsequent administration to a degree not observed after a single large dose.

Chart 1 represents the curves of elimination for the preparations of digitalis employed in this study. Dooley,[17] working in this labora-

17. Dooley, M. S.: Evidence for the Presence in Digitalis of a Principle that is Eliminated Rapidly After Intravenous Injection into the Cat, J. Pharmacol. & Exper. Therap. **17**:277, 1921.

tory, found evidence for the presence of a rapidly eliminated fraction in the tincture of digitalis from the observation that more was required by slow than by rapid injection to cause death. Weiss and Hatcher[18] subsequently described the isolation of this fraction. In another way, then, the presence in the tincture of digitalis of a rapidly eliminated fraction is confirmed. The general behavior of this fraction is also confirmed; individuals vary in their capacity to eliminate it; its quantity varies with different preparations. In one preparation, 20 per cent. of the original dose was eliminated in from three to four hours; in three others, as much as 40 to 50 per cent. of the activity of the initial dose was eliminated in the same length of time.

The curves were not continued to obtain 100 per cent. elimination. While there is abundant evidence that small fractions of action or effect persist beyond the limits indicated, the method is not sufficiently exact to determine them. The general principles, nevertheless, stand out clearly. As for a single preparation, after a large intravenous dose there is rapid elimination at first, a secondary rise in toxicity, followed by a more gradual decline of action. The persistence at the end of twenty-four hours is no index of the behavior of the preparation over longer periods of time. At the end of one day, the persistence of two preparations may be practically the same; at the end of two days, about 50 per cent. of one of these may be eliminated, while about 85 per cent. of the other may be eliminated. Again, at the end of two days, the persistence of two preparations may be practically the same, while at the end of four days about 40 per cent. of one may be eliminated and about 90 per cent. of the other. It is evident, therefore, that the curve of digitalis persistence is not a simple one, that it varies with different tinctures, and that the ultimate persistence of action of one tincture may be several times longer than that of other tinctures.

The specimen of the fraction obtained after ether extraction behaved in a manner similar to that of the ordinary tincture (Table 5).

The meaning of this peculiar curve of digitalis elimination and its variations with the different tinctures find an explanation in facts relating to digitoxin and the rapidly eliminated fraction. A dose of the latter that will kill in a few minutes is generally about the fatal dose or slightly more. The dose of digitoxin that kills in a few minutes is considerably larger than the fatal dose.[10] Much smaller doses will be fatal after the lapse of a day or after a longer time. Thus, 0.8 mg. per kilogram by vein was the dose of our specimen of digitoxin that killed at once. A dose of 0.3 mg. per kilogram by vein was given to

18. Weiss, S., and Hatcher, R. A.: Study of a Digitalis Body Which is Eliminated Rapidly After Its Intravenous Injection in the Cat, J. Am. Pharm. A. **12**:26, 1923.

a cat. On the following day, it showed extreme depression, and only 8 per cent. of a fatal dose of ouabain caused death. These facts support the data given in Table 5 that the effects of a fairly large dose of digitoxin that does not kill immediately may show a progressive increase. It has already been indicated, also, that from the standpoint of elimination these two fractions stand at opposite extremes. That neither substance is pure appears quite certain. That they exist in the leaf in the form in which they are extracted is considerably less certain. All one can say is that digitalis yields, in variable amounts, these two substances which show to a variable degree these entirely different tendencies: one develops its full action in a few minutes and shows almost no persistence after a short time; the other is capable of showing a progressively increasing effect and almost complete persistence after a similar length of time. The resultant of these forces, one rising, the other falling, is exhibited in the more complex and variable curve of digitalis elimination.

Throughout the work our attention has been called to the not infrequent occurrence of delayed death following large doses of the digitalis bodies. The failure to include deaths after the first day in the calculations is not intended to imply that such deaths may not in a number of cases have been due directly to the action of the drug. Let us recall here a few observations relating to this question. The rise in intensity of digitoxin action has already been referred to; also, the occurrence of death as long as four days after the administration had been stopped (Animal *B*). The rise in intensity of action appeared to be more marked with repeated small injections than with a single large one (Animals *E* and *F*); it resulted in death when the dose approached, presumably, rather closely the fatal amount (Animals *C*, *E*, *F* and *G*). The last doses were frequently not followed by emesis. The largest number of delayed deaths occurred with that preparation that showed the closest digitoxin-like behavior (Table 1). There were no late deaths with the preparation that showed the least digitoxin-like action (Table 2).

It is of some interest to consider the part played by the digitoxin-like fraction of digitalis in the cases of late death following the administration of large doses of the drug. It is of greater importance to consider the possible clinical bearing of the facts presented above. It is undoubtedly true that, with proper usage, deaths from digitalis are exceedingly uncommon. Considerably less common are deaths following digitalis administration in which definite causal relation has been established by the electrocardiogram. The occurrence of death soon after the administration of the drug in a patient whose previous condition gave no reason to suspect impending death is generally taken as the essential evidence when a causal relation is suspected. But it is

not rare to find cases with this clinical history (two such have recently been seen by the writer). After more or less continuous administration of digitalis for months or years with occasional emesis from overdigitalization, there are suddenly toxic signs in the form of disordered rhythm—frequent extrasystoles, coupling, etc.—whereupon the drug is discontinued. There is no vomiting at this time. The general condition may or may not seem worse. The patient dies suddenly, days after the last dose of the drug. In view of the fact that sudden death may occur in patients suffering from chronic cardiac disease, attributed generally to embolism or coronary thrombosis—in some cases observed postmortem, in other cases surmised—one can say nothing positively about the rôle played by digitalis. The facts stated above, however, suggest a possibility that deserves more careful investigation.

THE CLINICAL PROBLEM

The need for standards in digitalis therapy has been felt particularly by those clinicians who have had large numbers of patients with cardiac disease under their care. A long stride was made by the advent of the cat unit determination of activity [11] and the application of this unit to digitalis dosage in man.[19] Expressed in terms of activity, much confusion in digitalis dosage has been reduced to relative order. While it is commonly recognized that activity and not quantity is the rational basis for administration, it seems less commonly appreciated that in point of standardizing the drug, activity is only one third of the problem. Preparations of high degree of activity when tested by intravenous injection but practically inert by mouth in man,[20] due presumably to failure of absorption or too rapid elimination, are reported.[21]

Pardee [22] investigated the subject in man with one specimen, determining elimination as has been done experimentally, in terms of persistence of action, arriving at the conclusion that the average daily elimination of digitalis in man is 22 minims of the tincture. The activity of his preparation, he reports, was 1.25 c.c. of the tincture to the cat unit. Expressed in terms of a preparation with a cat unit of 0.75 c.c., the average daily elimination should be about 13 minims of the tincture. I have observed about seventy-five patients suffering with chronic cardiac disease and heart failure, requiring on the average about 30 minims a day of a preparation with the latter activity in order

19. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.
20. Wedd, A. M.: Observations on the Clinical Pharmacology of Digitalis, Bull. Johns Hopkins Hosp. **30**:131 (May) 1919.
21. Eggleston, C., and Wyckoff, J.: The Absorption of Digitalis in Man, Arch. Int. Med. **30**:137 (Aug.) 1922.
22. Pardee, H. E. B.: Notes on Digitalis Medication, J. A. M. A. **73**:1822 (Dec. 13) 1919.

to maintain optimum improvement over weeks and months. It is obvious that one cannot say whether absorption or elimination accounts for the fact that one preparation required two and a half times the dose of the other in point of activity to maintain digitalization.

An interesting light is thrown on the subject by the extreme variations in the reports of the persistence of various digitalis phenomena. Eggleston [13] reports heart block lasting from three to six days. Bastedo [23] reports heart block lasting three and one-half weeks. Kay [24] found that the slowing in auricular fibrillation persisted from three to five days after administration of the drug by the high dose method. Robinson [25] found this slowing to last from four to fifteen days, with an average of nine days. These clinical data seem strikingly in accord with evidence given in Chart 1. We are aware of the numerous factors that might conspire to produce these variations—the nature of the heart condition, the end point for observation, the total dosage, etc. These facts, nevertheless, in the light of observations recorded in this study, make it difficult to escape the conclusion that the problem of digitalis persistence in man cannot be disposed of with one preparation. That departures from an average, so determined, represent merely individual variations of susceptibility, and elimination fails to take cognizance of a simple but fundamental fact—in behavior and composition, different specimens of digitalis vary. That this fact applies not only to activity and absorption, but also to elimination, experimental evidence shows and clinical observation seems to confirm. We should state here that one does not escape the difficulty by employing a preparation always made by the same manufacturer. Though the activity may be the same, different lots of the tincture being prepared from different lots of the crude drug will in all probability vary in their rates of elimination.

The application, without evidence, of results obtained with one species to another is indeed a fruitful source of confusion in the study of digitalis. Pardee [22] states: "It is evident that the animal experiment would not give a definite answer to the question of the rate of disappearance of the drug, because of the marked variations that were found between different species." But as marked as are the variations between certain species, as striking seems to be the similarity in the behavior, in some respects, of the cat to man toward some of the digi-

23. Bastedo, W. A.: The Signs of Overdosage in Digitalis Administration, Am. Practitioner **46**:609, 1912.

24. Kay, W. E.: The Rapid Administration of Digitalis in Cardiac Decompensation, California State J. M. **17**:329, 1919.

25. Robinson, G. C.: The Rapidity and Persistence of the Action of Digitalis on Hearts Showing Auricular Fibrillation, Am. J. M. Sc. **159**:121, 1920.

talis bodies.[26] In the cat, strophanthin is comparatively more rapidly eliminated than digitalis. In man, a similar relation between strophanthin and digitalis is reported. Cohn and Levy [27] found, in man, that the effects of the former rarely last more than five days, while the effects of the latter generally persist more than ten days. Again, Hatcher [28] showed that the chloroform-soluble fraction of digitalis was readily absorbed from the gastro-intestinal tract of the cat. Eggleston and Wyckoff [21] observed a similar behavior toward this fraction in man. The clinical bearing of the differences found experimentally in the rate of elimination of the different digitalis preparations requires further study. The electrocardiogram may help to solve the problem. Should a relation be established, the problem of digitalization and its maintenance with a minimum of toxic reactions may be brought one step further within control.

SUMMARY

A. Experimental.—1. A brief review of the literature relating to the fate of the digitalis bodies in the animal organism is given.

2. The results of a study of digitalis elimination in the cat are reported in terms of persistence of action.

3. The rate of elimination of digitalis varies with different specimens; the persistence of one may be several times that of another.

4. Tolerance to the digitalis bodies probably depends on two factors: (1) tissue immunity and (2) capacity for elimination.

5. The digitalis bodies can produce an effect that persists independently to a degree of the presence of the drug.

6. Digitoxin produces an effect that for a short time increases in intensity.

7. The rapidly eliminated fraction does not exhibit this rising effect.

8. The curve of digitalis elimination is complex and variable, depending on the resultant of action of the rapidly eliminated and the digitoxin-like fractions.

9. The persistence of digitoxin as tested by the method of repeated dosage is considerably longer than that of the ordinary tincture of digitalis.

10. Repeated doses of digitoxin or digitalis appear to sensitize to subsequent action of the drug. The suggestion is offered that potentiation may, in part, account for so-called cumulation.

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26. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. M. **29**:485, 1919. Also Footnote 9.

27. Cohn, A. E., and Levy, R. L.: A Comparison of the Action in Patients of G-Strophanthin and Digitalis, Proc. Soc. Exper. Biol. & Med. **17**:81, 1920.

28. Hatcher, R. A.: Some Observations on the Pharmacology of a Digitalis Body, J. A. M. A. **75**:460, (Aug. 14) 1920.

11. The relation of delayed death following digitalis to the digitoxin-like fraction is discussed.

12. In a starving animal, 0.1 mg. of ouabain per kilogram is the fatal dose if the calculation is made on the basis of the average of the original and the new weights.

B. Clinical.—1. Evidence is given to show that to determine elimination of digitalis in man several specimens must be employed.

2. Clinical reports of digitalis persistence are strikingly in accord with experimental results and seem to indicate that, in man, tinctures of digitalis obtained from different sources are eliminated at different rates.

3. The clinical significance of late digitalis death is set forth. The possibility of its occurrence days after the cessation of administration of the drug is suggested.

4. Evidence is cited to show that the cat behaves in many respects similarly to man toward some of the digitalis bodies. The importance of an index of elimination in the standardization of the digitalis bodies for the more precise control of digitalis action is indicated.

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OBSERVATIONS ON THE EFFECTS OF INSULIN IN THE TREATMENT OF DIABETES MELLITUS *

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My object is to present the data obtained in a number of cases of diabetes mellitus following the administration of insulin. (These observations were made possible through the generosity of the diabetic committee of the University of Toronto who supplied this hospital with approximately 400 units of the extract weekly.) The first experience we had was with a patient with severe diabetes, and it was soon found that the weekly supply of insulin would be sufficient to treat intensively only about one case a week. For this reason the greater part of the insulin was applied to the study of various problems concerning the diabetic patient, and in only emergency cases was there any serious attempt made at treatment. A number of patients with severe diabetes previously discharged were, therefore, readmitted for observation.

I record the following observations:

1. Effect of insulin on a case of incipient diabetic coma with recovery
2. Blood sugar time curves showing effect of insulin on the rate of fall of the sugar content of the blood
   - (*a*) Two hour curves
   - (*b*) One hour curves
   - (*c*) Fifteen minute curves
3. Effect of insulin on the blood sugar and acetone bodies, plasma carbon dioxid combining power, urinary excretion of sugar and ammonia, noted at short intervals
4. Effect of insulin on the respiratory quotient
   - (*a*) Average curve made from the respiratory quotients of twenty-four diabetic patients plotted with respect to glucose tolerance
   - (*b*) Curve of the daily respiratory quotients of a patient with severe diabetes treated with insulin
   - (*c*) Comparison of (*a*) with (*b*)
   - (*d*) Respiratory quotient time curve following ingestion of glucose in a diabetic patient
   - (*e*) Blood sugar time curve following ingestion of glucose in a diabetic patient
   - (*f*) Effect of insulin on (*d*) and (*e*) in the same person
5. Course of a patient on a diabetic diet, with and without insulin; in all the work the technical methods employed were:

Blood: Sugar—Lewis-Benedict method
Acetone bodies—Van Slyke method
Plasma carbon dioxid—Van Slyke method
Urine: Sugar, qualitative—Benedict method
Quantitative—Benedict method for large amounts
Benedict-Osterberg method (1921) for small amounts
Total organic acid: Van Slyke and Palmer methods

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* From the Department of Metabolism of the Montreal General Hospital.

EFFECT OF INSULIN IN A CASE OF INCIPIENT DIABETIC COMA WITH RECOVERY

The effect of insulin on the clinical course of one case studied was so striking that it is worthy of note:

A girl, aged 12, with a history of acute diabetes of three months' duration was admitted at 1 a. m., Dec. 2, 1922, into the service of Dr. H. A. Lafleur, practically in coma. The urine markedly reduced Benedict's solution and gave a strong Ferric chlorid reaction for diacetic acid. The blood sugar was enormously increased (0.785 per cent.). The plasma carbon dioxid combining power was 19.1 per cent. by volume. Sixteen units of insulin were immediately administered, and the blood sugar, plasma carbon dioxid, urine sugar and acetone

TABLE 1.—*Course of Author's Case, Case 6109*

Date	Time	Blood Sugar Percentage	Plasma Carbon Dioxid per Cent. by Volume	Remarks
12/ 2/22	1 a.m.	0.781	19	Incipient coma
		16 units insulin		
	8 a.m.	0.561	24	Drowsiness less marked
	7 a.m.	0.310	28	Drowsiness less marked
		16 units insulin		
	11 a.m.	0.272	32	
	7 p.m.	8 units insulin		
12/ 3/22	9 a.m.	0.434	24	16 units 11 a.m. and 6 p.m.
12/ 4/22	9 a.m.	0.294	46	8 units 9 a.m.
12/ 5/22	9 a.m.	0.230	49	8 units 7, 11, 4; meals 9, 1, 6 (Woodyatt basal)
12/ 6/22	9 a.m.	0.185	52	8 units 7, 11, 4; meals 9, 1, 6 (Woodyatt basal)
12/ 7/22	9 a.m.	0.143	54	8 units 7, 11, 4; meals 9, 1, 6 (Woodyatt basal)
12/ 8/22	9 a.m.	0.085	..	8 units, 7, 11, 4; meals 9, 1, 6 (Woodyatt basal)
12/ 9/22	9 a.m.	0.226	..	No insulin given
12/10/22	9 a.m.	0.147		
12/11/22	9 a.m.	0.109		
12/12/22	9 a.m.	0.180	..	Taken 1½ hours after breakfast
12/13/22	9 a.m.	0.132		
12/14/22	9 a.m.	0.100		
12/17/22	9 a.m.	0.120		
12/19/22	9 a.m.	0.120		
12/22/22	9 a.m.	0.121		
12/23/22	9 a.m.	0.119	..	Discharged

bodies studied periodically as shown in Table 1. At 7 a. m., six hours after the beginning of the treatment, during which two doses of insulin were administered, the drowsiness had practically disappeared. No food nor fluids of any kind, except water, were given during the next two days. The clinical picture was that of gradual improvement, and corresponding with this, improvement was shown by the laboratory data. On Dec. 5, 1922, there was only a trace of acetonuria, and the child appeared to be out of any immediate danger of coma. There was still some glycosuria. A basal Woodyatt diet was then given, and small doses (8 units) of insulin administrated three times a day, two hours before each meal. On Dec. 7, 1922, the blood sugar was normal, the plasma carbon dioxid was normal, and the urine was free from sugar and acetone bodies. The insulin was then discontinued. Observations made daily during the following week on the blood and urine showed normal values, except for a slight degree of hyperglycemia, which eventually disappeared. The child was discharged from the hospital on Dec. 22, 1922. Since then five weeks ago,

she has gained 10 pounds (4.5 kg.), and the urine has remained sugar free and acetone free. The blood sugar examined weekly since has been normal. Chart 1 shows graphically the course of the case in detail. Table 1 shows the actual figures in detail.

EFFECT OF INSULIN ON THE RATE OF FALL OF THE BLOOD SUGAR

A series of cases were studied with reference to the effect of insulin on the degree and rate of fall in the blood sugar. In all cases a constant amount of insulin was given (16 units). In Table 2 are given the

TABLE 2.—*Blood Sugar Following Administration of Insulin*

Case Number	Units	Basal Period	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	14 Hours
6163	16	0.239	0.129	0.084	0.081	0.094	0.167	.....
5831	16	0.212	0.204	0.168	0.166	0.144	.....	0.232
5157	16	0.180	0.181	0.136	0.086	.....	.....	0.200
6197	16	0.195	0.120	0.126	.....	0.180	.....	.....
6109	16	0.781	0.561	0.310	.....	.....	.....	.....
6163	8	0.167	0.052	.....	.....	.....	.....	.....

			1 Hour	2 Hours	3 Hours	4 Hours	5 Hours
6197	16	0.200	0.152	0.120	0.100	0.126	0.129

			15 Min.	30 Min.	45 Min.	60 Min.	75 Min.	90 Min.
6451	16	0.235	0.226	0.185	0.152	0.148	0.098	0.086
6397	16	0.276	0.245	0.214	0.210	0.194	0.115	0.082

TABLE 3.—*Effect of Insulin on Blood Sugar*

Case Number	Blood Sugar 1	2	3	Units	Weight, Kg.	Glucose Tolerance, Gm.	Fall in Blood Sugar: Mg. per Kg.	Mg. per Unit
6109	0.781	0.561	0.230	16	38.0	30	5.71	13.7
5831	0.212	0.204	0.008	16	60.0	25	0.13	0.5
6397	0.277	0.115	0.162	16	58.0	40	2.76	10.1
6451	0.235	0.006	0.139	16	50.0	41	2.78	8.6
6197	0.194	0.120	0.074	16	72.7	52	1.01	4.6
5157	0.185	0.136	0.049	16	59.0	67	0.83	3.0
6163	0.239	0.129	0.110	16	44.3	75	2.48	7.8
	0.167	0.052	0.115	8	....	..	2.59	14.3

detailed results, and these are represented graphically in Chart 2. Blood sugar estimations were made in four cases every two hours, in one case every hour and in two cases every fifteen minutes. The temporary effect of insulin is shown in the two hour curves. That an immediate effect is obtained is shown in the fifteen minute curves. An attempt was made to determine whether the fall in the blood sugar was directly related to the body weight, dose of insulin or severity of the disease. The index of the latter was taken as the glucose tolerance determined by the Woodyatt method ($G = C + 0.1\ F + 0.58\ P$). In Table 3, it will be noted that no correlation could be found in the cases studied. This at the time of the observations was attributed to the

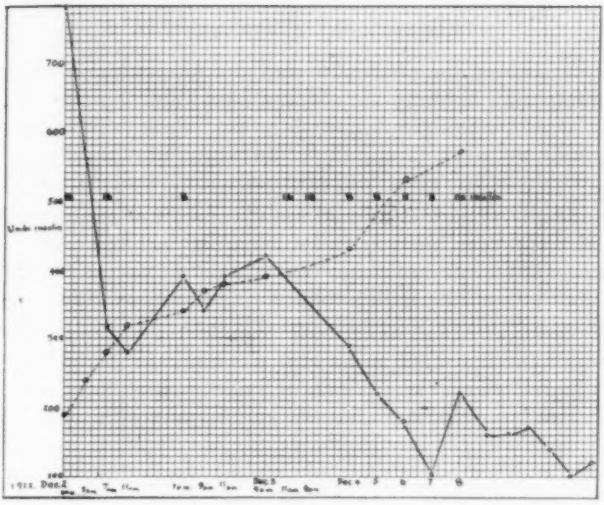

Chart 1.—Incipient diabetic coma. The continuous line is the blood sugar curve, per cent. divided by 1,000; the broken line is the plasma carbon dioxid curve, per cent. divided by 10. Insulin was given to the patient as follows: on the sixth and seventh, 8 units were given at 7 and 11 a. m. and at 4 p. m.; on the eighth, 8 units were given at 7 a. m. only.

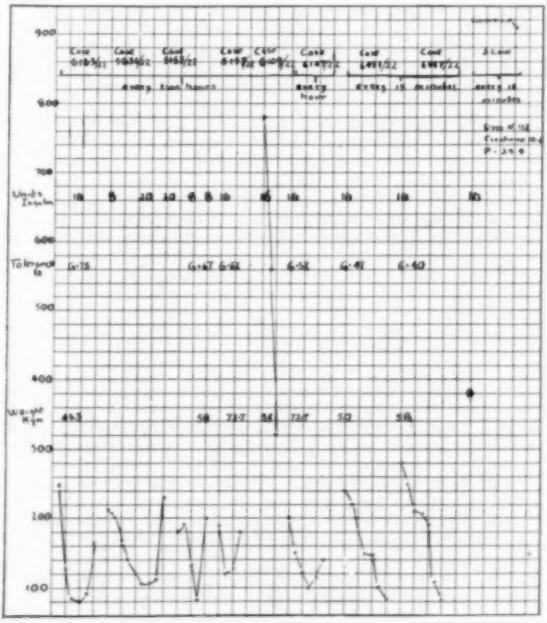

Chart 2.—Blood sugar time curves following the administration of insulin. The blood sugar is divided by 1,000.

possible variation in the potency of the individual preparations used. This was strongly suggested in the last case, No. 6163, in which 8 units produced practically the same fall that 16 units produced in the same person one week previously. The latter result was, however, attributed by Dr. Banting[1] to the fact noted by him, that the effect of insulin may vary in the same person at different stages in the treatment. In one patient (J. Low) admitted in the last stages of diabetic coma, no change was noted in the blood sugar following the administration of 50 units of known potent preparation. This case was, however, complicated by surgical lesions of both kidneys associated with complete anuria. The blood urea nitrogen was 112 mg. per 100 c.c., creatinin 10.2 mg. and phosphorus 29.4 mg. per 100 c.c. of blood. This may partly explain the enormous degree of hyperglycemia—1,000 per cent. Blood sugar estimations made every ten minutes for one hour showed practically no fall. The patient died one and one-half hours after admission to the hospital.

EFFECT OF INSULIN ON THE BLOOD SUGAR AND ACETONE BODIES, PLASMA CARBON DIOXID COMBINING POWER, URINARY EXCRETION OF AMMONIA AND SUGAR AND THE RESPIRATORY QUOTIENT

Since a definite fall in the blood sugar was noted every fifteen minutes, observations were then made on a severe diabetic patient (Woodyatt G = 40) at short intervals on the effect of insulin on the

TABLE 4.—*Effect of Insulin on a Patient with Severe Diabetes, Case 6397*

Time	Respiratory Quotient	Titrable Acid Plus Ammonia C.c. N/10	Urine Sugar, Gm.	Blood Sugar Percentage	Plasma Carbon Dioxid, Percentage by Volume	Blood Acetone Mg. per 100 C.c.	Remarks
9:30	0.724	..	.....	0.277	39.3	104.2	16 units insulin
9:45	0.750	41	0.596	0.243	39.6	86.7	
10:00	0.764	36	0.640	0.217	40.2	72.6	
10:15	0.782	30	0.482	0.212	40.8	74.3	
10:30	0.786	38	0.276	0.192	42.4	56.4	
11:30	0.796	54	0.107	0.115	42.2	43.8	
12:30	0.804	37	0.177	0.080	44.4	39.3	

blood sugar and acetone bodies and plasma carbon dioxid combining power, urinary excretion of sugar and ammonia and the respiratory quotient. (The technic of determining the latter, and the precautions taken in the interpretation will be described under the section on the respiratory quotient.) The effect of the insulin in this case was almost immediate. In Table 4 are shown the detailed results, and these are

1. Personal communication.

graphically represented in Chart 3. The most rapid changes noted were in the fall of urinary excretion of sugar and titratable acid plus ammonia. The graphic chart suggests an increase of the latter during the second hour. If, however, the total of the four fifteen minute periods are added together, it will be noted that the excretion was much less during the second than during the first hour. The rise in the carbon dioxid combining power of the blood was not inversely in proportion to the fall in the excretion of titratable acid plus ammonia, nor to the fall of the concentration of acetone bodies in the blood. The body was thus apparently able to oxidize the acetone bodies much more rapidly than

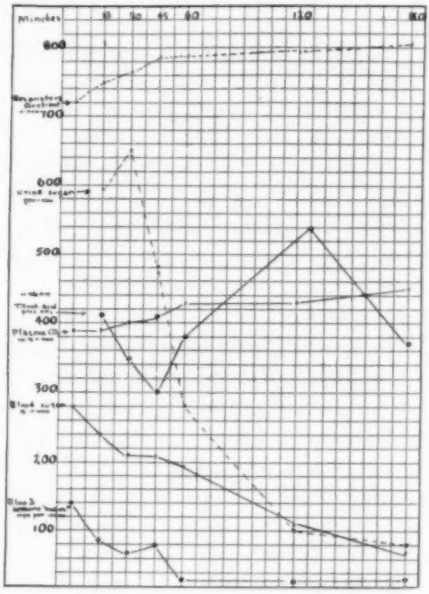

Chart 3.—Effect of insulin on blood sugar, blood acetone bodies, plasma carbon dioxid, urine sugar, urine acetone bodies and respiratory quotient.

it could mobilize alkali. When all other factors are considered which may effect a rise in the respiratory quotient during so short period determinations by indirect colorimetry, it is difficult to interpret the respiratory quotient curve obtained in this case. Since this diabetic patient had a severe acidosis, the rise in the respiratory quotient may be partly attributed to the oxidation of the acetone bodies.

RESPIRATORY QUOTIENTS

Some observations were then made on the respiratory quotients since the latter offers the best index to the replacement of fat and protein

metabolism by glucose. In a diabetic patient the interpretation of results obtained are complicated by the fact that the acetone bodies give approximately the same respiratory quotient as carbohydrate, fat and protein. Thus:

Substance	*Respiratory Quotient*
Carbohydrate	1
Diacetic acid	1
Protein	0.81
B-oxy-butyric acid	0.89
Fat	0.71
Acetone	0.75

In order to avoid this complication in the interpretation of results for these studies, the only diabetic patients observed were those whose urine was acetone free and plasma carbon dioxid normal. All determinations were made with the Tissot apparatus and half-face Siebe-Gorman mask. Gas analyses were made with the Haldane apparatus. In spite of the many disturbing factors which might influence the respiratory quotient by the method used, such as short period observations, abnormal breathing (mask), rapid washing out of carbon dioxid due to temporary increased pulmonary ventilation at the moment the venous punctures were made, etc., the results obtained are significant qualitatively of the effect of insulin on storage and utilization of sugar. It is generally accepted that a diabetic patient has no difficulty in obtaining sugar from the usual precursors; it is from the disproportion between formation, utilization and storage that the hyperglycemia results. The results obtained with insulin show that stroage plays a great part in the control of the hyperglycemia during the treatment with insulin.

The routine in the determination of all the respiratory quotients recorded here, with the exception of the time curves obtained following the ingestion of glucose, were made under the accepted standard conditions—in the postabsorptive state fifteen hours after the evening meal and after one-half hour of complete muscular rest.

In Table 5 is shown the average respiratory quotient obtained in twenty normal persons. During the last year some data were obtained concerning the relation between the glucose tolerance of the patient determined by the Woodyatt method ($G = C\,0.1\,F + 0.58\,P$) and the respiratory quotient obtained fifteen hours after the evening meal. The results are recorded in the same table. It will be noted that although in isolated instances a patient may show a greater respiratory quotient than another whose tolerance is greater (Cases 818 and 543),

if the cases are grouped with respect to their tolerance, for example, G = 50 — 75, 75 — 100, 100 — 125, etc., the tolerance for the group is greater, and a greater average respiratory quotient is obtained; that is, it is reasonable to assume the less severe the diabetes, the more the patient is able to store glycogen in the body and thus show a greater respiratory quotient in the postabsorptive state—fifteen hours after

TABLE 5.—*Average Respiratory Quotient Obtained in Normal Persons*

Normal Respiratory Quotients			Comparison of the Tolerance of Glucose With the Respiratory Quotient in Diabetic Persons			
Case Number	Basal Metabolic Rate	Respiratory Quotient	Case Number	Glucose Tolerance (Woodyatt)	Respiratory Quotient	
6427	4	0.816	1739	56	0.714	
6497	2	0.814	2602	58	0.792	
6353	6	0.836	4146	62	0.732	
6100	2	0.809	955	63	0.714	
6286	4	0.798	818	66	0.719	
5958	7	0.817	543	72	0.768	0.738
5741	9	0.842	5135	77	0.730	
5658	7	0.810	1157	82	0.764	
6210	3	0.826	30	84	0.729	
6068	2	0.836	844	85	0.742	
6148	2	0.767	252	96	0.782	
6100	2	0.827	704	98	0.803	0.758
6161	11	0.901	1193	104	0.796	
5751	5	0.834	352	114	0.794	
6063	2	0.906	1700	116	0.732	
5957	3	0.811	940	129	0.787	
4969	6	0.795	1154	132	0.823	
5621	5	0.831	5601	147	0.746	0.779
5792	3	0.759	2423	169	0.764	
5400	5	0.792	5642	216	0.826	
			2363	219	0.799	
			2968	235	0.838	
			5961	240	0.801	
Average.....		0.811	6055	242	0.814	0.807

TABLE 6.—*Results of Administration of Insulin in Case 6163*

	Respiratory Quotient	Remarks
Basal.....	0.752	No insulin
December 8.....	0.762	8 units 7 a.m.; test, 9 a.m.
9.....	0.748	No insulin
10.....	0.734	No insulin
11.....	0.778	8 units, 7 a.m.
12.....	0.769	8 units, 7 a.m.
13.....	0.784	8 units, 7 a.m.
15.....	0.761	8 units, 7 a.m.
16.....	0.779	4 units before meals
17.....	0.792	4 units before meals
18.....	0.798	4 units before meals
20.....	0.787	4 units 7 a.m. only
21.....	0.795	8 units 7 a.m. only

the evening meal. If this assumption is even approximately correct, a patient who can take more food while under the effects of insulin and can store part of it should show a greater quotient in the post-absorptive state if storage has actually occurred. The results obtained in the one case reported here suggests that there has been a storage of carbohydrates. In Table 6 will be seen the detailed results. The patient was kept under the influence of insulin for a period of two

weeks. His original tolerance before administration of insulin was 75 gm. glucose (Woodyatt). While under the influence of insulin the diet could be increased to a glucose tolerance of between 125 and 150. The respiratory quotient was determined daily. The results noted are graphically shown in Chart 4. Curve *A* represents that of the average respiratory quotient of the different groups of cases with respect to their tolerance of glucose, G = 50 — 75, 75— 100, etc., shown in Table 5. The dotted curve is that of the patient's daily respiratory quotient. It will be noted that at the end of two weeks the patient had acquired a respiratory quotient corresponding to that of a person whose tolerance would be approximately 175.

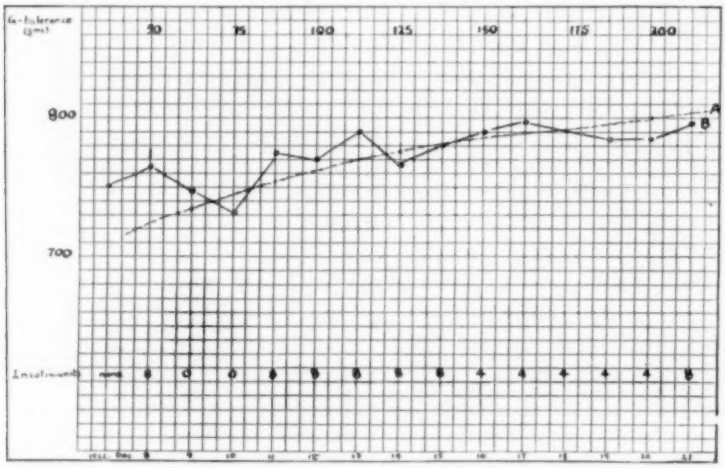

Chart 4.—Effects of tolerance for glucose and insulin on the respiratory quotient. *A* is the average curve; *B*, Case 6163. The respiratory quotient is divided by 1,000. On December 8, 8 units of insulin were given at 7 a. m.; on the eleventh, twelfth, thirteenth, fourteenth and fifteenth, 8 units of insulin were given at 7 a. m.; on the sixteenth, seventeenth, eighteenth, ninteenth and twentieth, 4 units were given three times a day, and on the twenty-first, 8 units were given three times a day.

That storage is a definite phenomenon observed under the influence of insulin is further demonstrated when the sugar tolerance and respiratory quotient time curves are corelated in the same person following the ingestion of glucose.

In the foregoing analyses all the respiratory quotient figures represent nonprotein values. In the following analyses in which sugar time curves were simultaneously obtained, the respiratory quotients were obtained directly without taking into consideration the protein

metabolism; that is, they were not of the nonprotein type. This is rather unfortunate. But the difficulty of obtaining a specimen of urine at the end of such small periods made the obtaining of nonprotein figures impossible. For practical purposes, however, this does not vitiate the results obtained, since qualitative values only were sought, a rise in the quotient indicating carbohydrate oxidation, etc.

The subject of one experiment had a mild diabetes. During the postabsorptive state and under standard conditions for basal metabolism studies, the respiratory quotient and blood sugar were determined. The

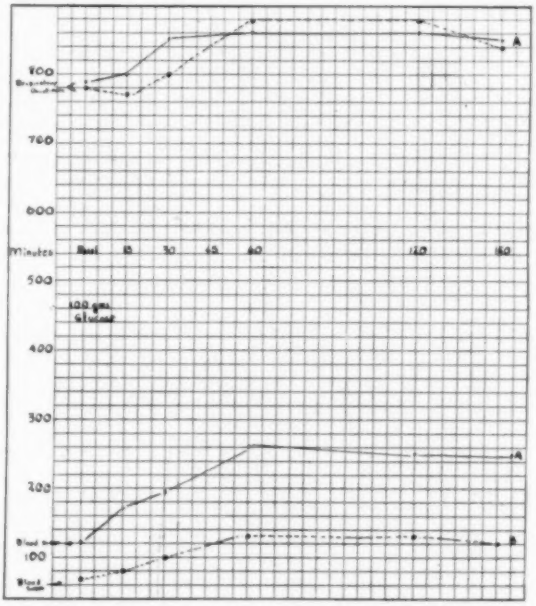

Chart 5.—Effect of insulin on blood sugar and respiratory quotient following ingestion of glucose in a "sugar free" diabetic patient. *A* indicates no insulin; *B*, 16 units of insulin one-half hour before ingestion of glucose; the blood sugar was divided by 1,000; respiratory quotient, 1,000.

subject was then given approximately 1.75 gm. of glucose per kilogram dissolved in 250 c.c. of water flavored with lemon. The face mask was then immediately adjusted, and the blood sugar and respiratory quotient estimations were made at the intervals stated in Table 7, which gives the detailed results. The time recorded represents the end of each experiment, the gas collection in the gasometer commencing ten minutes previously. In Chart 5 the results are recorded graphically. Curves *A*

represent a test during which no insulin was given. Curves *B* represent the results obtained in the same person a few days later, but one hour before the test 16 units of insulin were administered. Although the same dose of glucose was given in the second test, the blood sugar curve did not differ from that usually obtained in normal persons. In spite of this, there was no great change noted in the respiratory quotient curve. Storage is thus suggested. There is, however, a possibility of delayed absorption of the glucose from the alimentary tract. The fact that a rise in the quotient was obtained without insulin and that during

TABLE 7.—*Results of Administration of Insulin in a Patient with Mild Diabetes, Case 6497*

	Basal	15 Min.	30 Min.	60 Min.	120 Min.	150 Min.	180 Min.
Dec. 8, 1922—No Insulin Given							
Respiratory quotient	0.791	0.799	0.851	0.863	0.869	0.862	0.870
Percentage of blood sugar	0.121	0.172	0.196	0.200	0.250	0.247	0.240
Urine sugar	0	0	Trace	+	+	+	Trace
Dec. 15, 1922—Sixteen Units of Insulin Given One Hour Before Test							
Respiratory quotient	0.781	0.779	0.794	0.875	0.882	0.847	0.840
Percentage of blood sugar	0.071	0.060	0.098	0.130	0.130	0.119	0.114
Urine sugar	0	0	0	0	0	0	0

TABLE 8.—*Results of Administration of Insulin in a Patient with Severe Diabetes, Case 6163*

	Basal	10 Min.	30 Min.	60 Min.	90 Min.	100 Min.	130 Min.	160 Min.	190 Min.
Dec. 6, 1922—Sixteen Units Given at End of 90 Minutes									
Percentage of blood sugar	0.164	0.180	0.232	0.226	0.194	0.191	0.145	0.120	0.098
Urine sugar, gm.	.....	0.042	0.071	0.121	0.062	0.049	0.060	0.074	.....
Respiratory quotient	0.750	0.764	0.820	0.841	0.849	0.840	0.831	0.839	0.835
Dec. 13, 1922—Sixteen Units Given at End of 90 Minutes									
	Basal	10 Min.	30 Min.	60 Min.	90 Min.	100 Min.	130 Min.	160 Min.	190 Min.
	0.742	0.735	0.735	0.809	0.832	0.849	0.813	0.810	0.820

this rise the hyperglycemia persisted in the first test, suggests defective storage in the absence of insulin.

In Table 8 are recorded the results of the same experiment obtained in a patient with much more severe diabetes. In this case much less glucose was given, 25 gm., or 0.5 gm. per kilogram. A definite rise in the quotient was noted. In the fasting normal persons, judging from the literature on the subject, no rise occurs in the metabolism following ingestion of such small amounts of glucose on account of the retention of the latter in the organism in the form of glycogen. Even the rise occasionally noted has been attributed to the conversion of the carbo-

hydrates into fats, unaccompanied by actual combustion of carbohydrate. It was thought that the rise might be due to some of the factors mentioned before, for example, disturbance of the patient due to venous puncture, etc. It will be noted, however, that practically a corresponding rise (Curve *B*) was obtained in the same person at a later date when no venous punctures were made. In Chart 6 are recorded graphically the two curves—Curve *A* obtained during venous puncture and Curve *B* under more ideal conditions, that is, the glucose only was given and the respiratory quotient obtained at the stated intervals. It seems possible that a patient with severe diabetes will burn rather than store the little corbohydrate he is capable of tolerating.

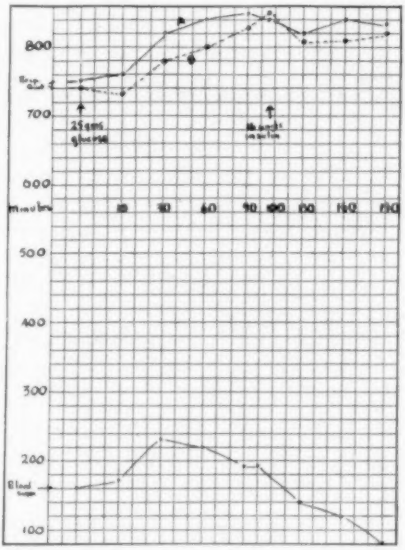

Chart 6.—Effect of insulin on blood sugar and respiratory quotient following ingestion of glucose in a "sugar free" diabetic patient. Curve *A* was taken during the blood sugar time curve determination; *B* was taken seven days later: the blood sugar was divided by 1,000; the respiratory quotient by 1,000.

Further studies of the effect of small doses of glucose on the respiratory quotient in the diabetic patients are now being undertaken in this hospital.

EFFECT OF DIET ON A PATIENT WITH SEVERE DIABETES WITH AND WITHOUT INSULIN

Chart 7 demonstrates definitely the possible sources of danger when diet and insulin are combined in the treatment, and impresses one with the important fact that insulin treatment has not yet reached the stage

where it can be applied in outside practice without being controlled carefully by laboratory analyses. The curve represents the course in a patient with severe diabetes (G, 45) who was discharged from the hospital in October, 1922. The urine was then sugar and acetone free. The blood showed only a slight hyperglycemia. The patient could be kept sugar free while on a Woodyatt diet, but was in a nutritional state much below normal. He was readmitted Dec. 10, 1922, to note the effect of insulin. Until December 16, the diet was the same as that which he was allowed on discharge. It will be noted that the total quantity of sugar excreted during the twenty-four hours was practically normal, about 1 gm., and only a slight hyperglycemia was present,

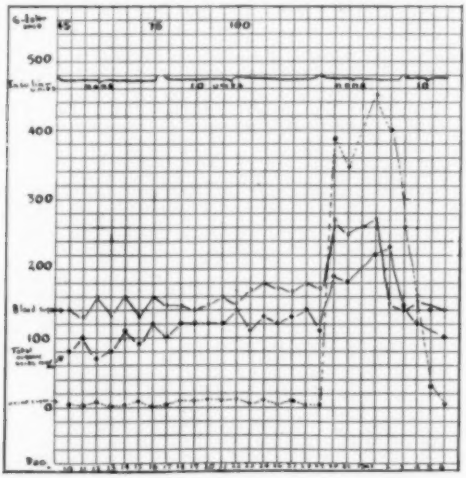

Chart 7.—Diet with and without insulin. The blood sugar was divided by 1,000; the urine sugar by 10; the total organic acids by 10.

approximately 0.150 per cent. Ten units of insulin were given three times a day, one hour before each meal, on December 16, and the diet was increased to G = 75. No great change was noted, either in the hyperglycemia or in the excretion of sugar. On December 23, the diet was further increased to G = 100. The same dose of insulin was continued. There followed an increase in the degree of hyperglycemia and a small increase in the excretion of sugar in the urine. On December 29, the supply of the extract was exhausted. The results which followed were striking. A marked hyperglycemia and glycosuria developed, and the excretion of organic acids increased. On Jan. 2, 1923, insulin treatment was again instituted, and the improvement in

the general condition of the patient and laboratory findings were just as marked. Thus the ability to utilize carbohydrates in this case was not due to an improved pancreatic function, but directly to the effect of the insulin.

DISCUSSION OF TREATMENT

The experience we have had demonstrates that the reaction of a series of patients with diabetes to insulin is not uniform. Injection of the extract isolated by the Toronto group of workers lowers the sugar content of the blood. It does so in such a manner as to enable the diabetic patient to metabolize more sugar. Thus it aids the complete oxidation of fat, preventing the formation of acetone bodies, or making them disappear when present. The effect, however, is temporary. Its chief value, in the present status of our knowledge of its action, seems to lie in tiding over the diabetic during the critical stage of the disease (precoma), so difficult to control with the usual procedures, fasting, intravenous injections of salines, etc. In patients with severe diabetes, emaciated, and in whom protein plays a great part in the formation of energy, and who progress best when controlled by a diet on the Woodyatt basis, with the administration of insulin the diet may be increased to the point where the patient gains weight and generally shows clinical improvement. Diet still remains the important means of controlling the disease. The ultimate type of treatment to follow, whether diet alone or diet plus insulin, seems to depend on whether the pancreatic function is completely destroyed as in pancreatic diabetes, or whether the little remnant is only temporarily overstrained, but can recover with rest. A case of the latter type seems to be the first one recorded here. The fact that the child has recovered under the effects of insulin, but does not now require the extract, diet alone sufficing, seems to prove that the pancreatic function was not completley destroyed but temporarily overstrained. The possibility of the development of "carbohydrate shock" associated with an hypoglycemia was emphasized by the Toronto workers. It has been suggested, where large doses of insulin are required, to give just sufficient of the latter to allow a constant slight trace of glycosuria. This, however, appears to be contrary to treatment that might lead to an improved pancreatic function. If traces of sugar are constantly present in the urine, it seems reasonable to assume that the full effect of the insulin given is made use of, but in spite of this the pancreatic function is also called on and strained. Allen has demonstrated that recuperation of pancreatic function can be negatived by overfeeding. Lack of thoroughness in relieving the food load is the chief factor in the deterioration of the little function left. The various responses obtained from insulin emphasize the statement of Sir John Rose Bradford that

diabetes is "a clinical label attached to a number of different conditions with varied origins, different morbid anatomy and physiology and liable to different courses." There is much more to learn of this disease. The efforts made and results obtained by Dr. Banting and his associates have opened a new field for study, but, most essential of all, they have resulted in the possibility of prolonging life and making it more worth living.